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PENICILLIN IN THE TREATMENT OF INFECTIONS

A REPORT OF 500 CASES

STATEMENT BY THE COMMITTEE ON CHEMOTHERAPEUTIC AND OTHER AGENTS, DIVISION OF MEDICAL SCIENCES, NATIONAL RESEARCH COUNCIL

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Our purpose in this report is to acquaint the medical profession with the results that have been obtained in the treatment of 500 cases of various infections with penicillin. All these cases have been treated by twenty-two groups of investigators[1] accredited to the Committee on Chemotherapeutic and Other Agents of the National Research Council, and the results of the treatment have been collected and summarized by the chairman of the committee, who acted for it and for the Committee on Medical Research. All the penicillin used in this study was provided by Merck & Company, E. R. Squibb & Sons and the Charles F. Pfizer Company. The costs of the penicillin were covered by a contract of the Office of Scientific Research and Development on the recommendation of the Committee on Medical Research. A recent statement of the progress of efforts with respect to penicillin has been published in THE JOURNAL by Dr. A. N. Richards, chairman of the Committee on Medical Research of the Office of Scientific Research and Development.[2]

The discussion of these 500 cases will be concerned with the over-all results in various groups of cases. Separate and detailed reports of cases will be made by the individual groups of investigators in due course of time.

SELECTION OF CASES FOR STUDY

In order to conserve valuable material and to gather as much information as possible in the shortest period of time, the committee restricted the use of penicillin to the treatment of the infections listed. It was necessary to limit both the number of patients treated and the types of infection to be studied, since only small amounts of penicillin were available for clinical investigation. It was the responsibility of the committee to direct the study toward those infections that are most likely to occur in our armed forces and to those that are resistant to the sulfonamides. The infections selected were:

1. Staphylococcus aureus bacteremia.
2. Local Staph. aureus infections failing to respond to the sulfonamides.
3. Streptococcic infections failing to respond to the sulfonamides.
4. Pneumococcic, streptococcic and staphylococcic meningitis or empyema.
5. Pneumococcic pneumonia failing to respond to the sulfonamides.
6. Sulfonamide resistant gonococcic infections.
7. Subacute bacterial endocarditis.

MODE OF ADMINISTRATION

In the present investigation solutions of penicillin were given intravenously, intramuscularly and topically, including local injection into the pleura, pericardium and joints and into the subarachnoid space. In giving penicillin intravenously, constant infusions were used in many cases, whereas repeated injections at two, three or four hour intervals were employed in others. When it became necessary to continue treatment over a period of several weeks, it was necessary in many cases to use various routes of administration, including constant intravenous infusion and repeated intravenous or intramuscular injections. Some patients tolerated intramuscular injections better than repeated intravenous injections; others did not.

In the treatment of meningitis, empyema and surface burns of limited extent, penicillin was used topically; that is, injected directly into the subarachnoid space or the pleural cavity or applied locally.

CONCENTRATION AND VOLUME OF PENICILLIN

For intravenous use, concentrations of 1,000 Oxford units per cubic centimeter or less were used at each injection. When a constant intravenous infusion was used the concentration was varied, depending on the total dosage during a twenty-four hour period. The rate of injection in some cases varied from 5,000 to 10,000 units an hour day and night; that is, 120,000 to 240,000 units every twenty-four hours. In others smaller amounts of solution were injected. This was regulated so that the rate of delivery was between 75 and 100 cc. an hour. The penicillin was dissolved in saline solution or 5 per cent dextrose solution and allowed to run into the veins slowly or injected directly into the rubber tubing at periodic intervals.

1. Accredited clinical investigators of the Committee on Chemotherapeutic and Other Agents, National Research Council: Dr. W. A. Altemeier, Cincinnati; Dr. Francis G. Blake, New Haven, Conn.; Dr. A. L. Bloomfield, San Francisco; Dr. M. H. Dawson, New York; Dr. Robert Elman, St. Louis; Dr. John Hirshfeld, Detroit; Dr. Frank Horsfall, New York; Lieut. Comdr. Adolph Hutter, Bethesda, Md.; Dr. Chester S. Keefer, Boston; Dr. J. S. Lockwood Philadelphia; Dr. Champ Lyons, Boston; Dr. J. F. Mahoney, Staten Island, N. Y.; Dr. Roy D. McClure, Detroit; Dr. C. F. McKhann, Ann Arbor, Mich.; Dr. Frank L. Meleney, New York; Dr. R. A. Nelson, Baltimore; Dr. F. A. Park, Baltimore; Dr. D. W. Richards, New York; Major George Robb, Washington, D. C.; Dr. David Smith, Durham, N. C.; Dr. Wesley W. Spink, Minneapolis; Dr. W. S. Tillett, New York; Dr. Barry Wood, St. Louis.

2. Richards, A. N.: Penicillin, J. A. M. A. **122**: 235 (May 22) 1943.

With intramuscular injections it is important to keep the volume as low as possible in order to avoid local discomfort at the site of injection. The usual practice has been to employ a concentration of 5,000 units per cubic centimeter. In general there was no local reaction, but there may be some local soreness at the site of injection in some patients.

DOSAGE

The total amount of penicillin administered in Oxford units has varied tremendously from one case to another. There were also many variations in the total amount given with each injection, the interval of time between injections and the total duration of the treatment. These are natural variables in the investigation of any new drug, especially when information is being accumulated with only a limited supply of valuable material in several different infections. At the beginning of our studies it was common practice to give 5,000 units intravenously every four hours day and night; that is, 30,000 Oxford units every twenty-four hours. This amount was found to be adequate in some infections but was totally inadequate in others. Indeed, the dosage schedule varied from 1,000 to 25,000 units per hour, depending on the kind and severity of infection. In view of the variation in the dosage schedule it will be well to outline the practice at the present time. Before presenting the details it should be said that the question of adequate or optimum dosage has not been clearly defined. The objective in treatment should be the maintenance of a sufficient concentration of penicillin in the blood to inhibit completely the growth of the individual infecting organism.

Various methods have been used to titrate penicillin in the blood serum and body fluids and exudates (Fleming,[3] Florey[4] and Rammelkamp[5]). They all have as their objective the determination of the amount of penicillin that will inhibit the growth of a constant number of a standard strain of hemolytic streptococcus or Staph. aureus or of the patient's own strain of infecting organism. When facilities are available, such methods should be employed in the treatment of individual cases in order to determine whether sufficient amounts of penicillin are being administered.

Other methods of assessing adequate dosage are the signs of clinical response. These must be followed with great care and should include not only the response of the temperature and pulse rate but also the change in constitutional symptoms, the results of blood culture and the effect on the local infection.

ABSORPTION, EXCRETION AND DISTRIBUTION

The absorption, excretion and distribution of penicillin has been studied by Rammelkamp and Keefer,[6] and the literature on the subject has also been reviewed by them. Blood concentrations of penicillin and urinary excretion of penicillin were determined after the administration of 5,000 to 40,000 Oxford units by various routes. Their summary was as follows:

Intravenous injection of penicillin resulted in high initial concentration in the blood plasma, which was followed by an abrupt fall. Traces of penicillin were found in the blood for thirty to two hundred and ten minutes after the injection, the length of time depending on the amount administered. The sharp fall noted in the serum concentration immediately after the injection was associated with an increased excretion in the urine. The average excretion after intravenous injection was 58 per cent of the administered dose.

Penicillin was rapidly absorbed when given intramuscularly and slowly absorbed after subcutaneous injections. Excretion in the urine was rapid following intramuscular injections and delayed after subcutaneous injections.

Absorption from the body cavities was delayed, and this was reflected in the slow excretion of penicillin by the kidneys. The total amount found in the urine was somewhat lower than that obtained following intravenous injection. Fluid aspirated from the pleural and joint cavities twenty-two and thirteen hours after the injection showed appreciable amounts of penicillin remaining.

Administration of penicillin by enteral routes showed that absorption from the duodenum was rapid, whereas oral and rectal doses were poorly absorbed. These findings may be explained by the inactivating effect on penicillin of acid and Escherichia coli. After oral, intraduodenal and rectal administration, the average amount excreted in the urine was extremely small.

In the presence of renal failure penicillin was not excreted rapidly, and as a result high concentrations were maintained in the blood stream after intravenous injections.

Studies on the distribution of penicillin showed that the substance failed to penetrate the red cells in significant amounts. In general the average concentration found in erythrocytes was less than 10 per cent of the plasma concentration. No penicillin was found in the spinal fluid, saliva or tears in subjects receiving it intravenously.

Rammelkamp and Helm[7] have shown that human saliva, bile and succus entericus do not inactivate penicillin, but gastric juice destroys it rapidly at body temperature. The destructive action appears to be due to hydrochloric acid and not to pepsin. In 2 patients with pernicious anemia and achylia gastrica the absorption of penicillin, when administered by mouth, was greater than that of normal subjects.

Aside from the excretion of penicillin in the urine, there is good evidence that it is excreted by the liver, since it can be found in the bile in higher concentration than in the blood stream. None has been demonstrated in the gastric juice.

INTRATHECAL INJECTION

With regard to the intrathecal injection of penicillin, in normal subjects the substance is slowly absorbed and slowly excreted in the urine following the injection of 5,000 or 10,000 Oxford units.[8] It may be detected in the spinal fluid for at least 31.5 hours after the injection of 10,000 Oxford units. There is some evidence that penicillin is slightly irritating to the normal meninges, and the injection of 10,000 Oxford units into the subarachnoid space may be followed by headache, vomiting, increased intrathecal pressure and pleocytosis in the spinal fluid. Smaller amounts cause less intense symptoms.

In patients with meningitis, absorption of penicillin from the intrathecal space is more rapid than in normal subjects, and a greater amount of that injection is excreted in the urine. Penicillin can be detected in the spinal fluid twenty-four hours after its injection.

3. Fleming, Alexander: An Antibacterial Action of Cultures of Penicillium, with Special Reference to Their Use in Isolation of B. Influenzae, Brit. J. Exper. Path. **10**: 226-236 (June) 1929.

4. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin, Lancet **2**: 177-189 (Aug. 16) 1941.

5. Rammelkamp, Charles H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol. & Med. **51**: 950 (Oct.) 1942.

6. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425 (May) 1943.

7. Rammelkamp, C. H., and Helm, J. D.: Studies on the Absorption of Penicillin from the Stomach, Proc. Soc. Exper. Biol. & Med., to be published; Excretion of Penicillin in Bile, ibid., to be published.

8. Rammelkamp, Charles H., and Keefer, Chester S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342-350 (March) 1943.

We have been unable to detect penicillin in the cerebrospinal fluid after intravenous or intramuscular injection; for this reason it is well for the time being at least to use penicillin both intravenously and intrathecally in the treatment of meningitis.

PENICILLIN RESISTANT STRAINS

It has been demonstrated by Rammelkamp and Maxon [9] that various freshly isolated strains of Staph. aureus vary only slightly in their susceptibility to the antibacterial action of penicillin. When, however, a given strain of Staph. aureus was grown in increasing concentrations of penicillin over a long period of time, it was possible to make the organism resistant. These investigators were also able to demonstrate that an increase in the resistance of Staph. aureus may also occur during the course of penicillin therapy for localized infections in man. Similar observations have been made by Florey and his collaborators [4] and by Blake.[10]

Others [11] have shown that strains of pneumococci, staphylococci and hemolytic streptococci may be made resistant to penicillin by exposing them to it continuously for a long period of time both in vitro and in vivo. It is of considerable interest that penicillin fast strains of pneumococci are susceptible to the sulfonamides and that sulfonamide resistant strains of pneumococci are susceptible to penicillin. Moreover, McKee and Houck [12] have shown that an increase in the resistance of organisms to penicillin is associated with a proportional loss of virulence, an observation that is in striking contrast to the retention of virulence by sulfonamide resistant cultures.

Obviously, more information is needed concerning penicillin resistant strains and their mode of production, since it may aid one in interpreting the clinical results or failure. It should be reemphasized that, once a strain increases in resistance, it loses its virulence and seems to be changed permanently as far as penicillin is concerned, but it remains susceptible to the sulfonamides. Also resistance is produced only after continuous exposure to the action of penicillin.

METHOD OF PREPARING PENICILLIN FOR TREATMENT

Penicillin is supplied in ampules of 5,000 units, 10,000 units, 25,000 units, 100,000 units and 1,000,000 units. As penicillin is extremely soluble, it may be dissolved in small amounts of sterile, distilled, pyrogen free water, in sterile isotonic solution of sodium chloride or in 5 per cent dextrose solution. When large unit sizes are being used in hospitals, the contents of the ampule should be dissolved in water or saline solution so that the final concentration is 5,000 units per cubic centimeter. This solution should be stored under aseptic precautions in an ice box and made up freshly every day. Solutions for local or parenteral use may be diluted further, depending on the concentration desired.

A. *For intravenous injection:*

1. The dry powder may be dissolved in sterile isotonic solution of sodium chloride in concentrations of 1,000 to 5,000 units per cubic centimeter for direct injection through a syringe.

2. The dry powder may be dissolved in sterile saline solution or 5 per cent dextrose solution in lower dilution (25 to 50 units per cubic centimeter) for constant intravenous therapy.

B. *For intramuscular injection:*

1. The total volume of injections should be small; that is, 5,000 units per cubic centimeter of isotonic solution of sodium chloride.

C. *For topical application:*

1. The powdered form of the sodium salt is irritating to wound surfaces and should not be used.

2. Solutions in isotonic solution of sodium chloride with a concentration of 250 units per cubic centimeter are satisfactory. For resistant or more intense infections this concentration may be increased to 500 units.

RESULTS OF TREATMENT

Staphylococcus Aureus Infections with Bacteremia.—There were 91 patients with Staph. aureus bacteremia. Death occurred in 34 cases (37 per cent) and no demonstrable effect was reported in 3 (3 per cent). In the remaining 54 cases there was complete recovery or striking improvement. All treated cases were included regardless of the amount of penicillin administered or the duration of the treatment. By present standards of treatment we know that many of these patients were inadequately treated with respect both to the total amount of penicillin they received and to the total duration of the treatment. A number of the patients were treated early in the course of our studies when very small amounts of material were available and when less was known about the dosage. It is well, therefore, to discuss separately the patients who recovered or improved and those who died or failed to improve.

It is well known that Staph. aureus infections with bacteremia are always serious and carry a high fatality rate. The outcome in any instance is influenced somewhat by the age of the patient, the site of the infection and its accessibility to surgical drainage, and the presence or absence of other debilitating diseases.

Patients with the most favorable outlook, then, are those under 40 years of age who have an infection localized in an area that can be drained surgically. Patients with the most unfavorable outlook are those over 40 years of age or with an infection that fails to localize or cannot be drained surgically, and those with other associated diseases. Another important point in prognosis is the duration of the illness. It is well established that in most cases of fatal staphylococcic infection death occurs within ten to fourteen days after the onset of the bacteremia.

With this information as a background, it might be expected that the patients who will receive the greatest benefit from penicillin are those under 40 years of age without complicating diseases who are treated intensively early in the course of their infection.

Cases with Recovery or Improvement.—Fifty-four (60 per cent) of the 91 patients in this group recovered or improved in a striking manner during treatment, so that recovery followed later. Thirty-six of these patients were under 40 years of age and 42 were under 50 years of age. The fatality rate in patients under

9. Rammelkamp, Charles H., and Maxon, Thelma: Resistance of Staphylococcus Aureus to the Action of Penicillin, Proc. Soc. Exper. Biol. & Med. 51: 386-389 (Dec.) 1942.

10. Blake, Francis G.: Personal communication to the Committee on Chemotherapeutics and Other Agents, National Research Council.

11. McKee, C. M., and Houck, C. L.: Induced Resistance to Penicillin of Cultures of Staphylococci, Pneumococci and Streptococci, Proc. Soc. Exper. Biol. & Med. 53: 33 (May) 1943. Schmidt, L. H., and Sesler, C. L.: Development of Resistance to Penicillin by Pneumococci, Proc. Soc. Exper. Biol. & Med. 52: 353 (April) 1943.

12. McKee, C. M., and Houck, C. L.: Induced Penicillin Resistance in a Pneumococcus Type III Culture, Federation Proceedings 2: 100 (March 16) 1943.

40 was 34 per cent, whereas in those over 40 it was 50 per cent. Forty-seven patients received penicillin for seven to twenty-one days, the average amount given being in the neighborhood of 500,000 Oxford units and the extreme ranges being 100,000 units in several infants and 3,465,000 units in some adults. As shown in table 2, there was recovery or improvement in 18 of 22 patients with acute osteomyelitis, in 9 of 10 patients with bacteremia without obvious port of entry, and in all 10 patients with infections of the skin and subcutaneous tissues. There were a number of other serious staphylococcic infections with bacteremia in which recovery or improvement took place (pneumonia, epidural abscess, burns, cavernous sinus thrombosis and meningitis).

Fatal Cases.—There were 34 fatal cases of Staph. aureus bacteremia. Fifteen of these patients (44 per cent) were over 40 years of age. Nine patients had acute bacterial endocarditis established at the beginning of treatment. They were treated over varying periods of time from four to fifty-two days and received from 270,000 to 2,340,000 units of penicillin. In no case was there even temporary improvement. In no case of Staph. aureus infection reported so far has endocarditis developed after treatment has been started.

Three of the patients who died had bilateral suppurative pyelonephritis. They were all elderly. One of them had diabetes and bilateral perinephric abscesses and was treated only two days before death. Another patient received only 35,000 units on the day of death.

Three patients had extensive burns—that is, more than 50 per cent of the body surface—with infection and bacteremia. There were a wide variety of disorders in which the staphylococcic infection was only contributory and was controlled by the penicillin but in which death resulted from the primary disorder (aplastic anemia, uremia from sulfadiazine administration, pulmonary embolism, cancer of rectum and so on).

These fatal cases emphasize once again the seriousness of Staph. aureus bacteremia in patients over 40 years of age, those with bacterial endocarditis and those with debilitating diseases. They also serve to stress the fact that early and adequate treatment is necessary to control infection.

Conclusions.—In brief, 60 per cent of 91 patients with Staph. aureus bacteremia recovered or improved under treatment, so that recovery followed later. Death occurred in 37 per cent, and no effect was observed in 3 per cent. In a group of such infections in which the fatality rate is so high, these results are very impressive, since the over-all fatality rate in this group without penicillin or sulfonamides is usually about 85 per cent. The results of penicillin treatment become more impressive when one remembers that among the fatal cases there were 9 cases of endocarditis and that 15 of the patients received treatment for less than seven days. Many were treated late in the course of the disease or received an inadequate amount of penicillin according to present standards of dosage. The failures only serve to emphasize the great importance of early diagnosis and immediate and adequate treatment. Adequate treatment should consist in giving enough penicillin to sterilize the blood and localize the infection, and in continuing it until signs of active infection disappear. This frequently requires between 500,000 and 1,000,000 units given over a period of seven to fourteen days or longer.

STAPHYLOCOCCUS AUREUS INFECTIONS WITHOUT BACTEREMIA

There were 137 patients with local staphylococcic infections without bacteremia treated with penicillin. Of these, 109 (80 per cent) recovered or improved, 11 (8 per cent) died and 17 (12 per cent) showed no demonstrable effect.

The various groups represented herein will be discussed separately.

Osteomyelitis.—Of the 55 patients with osteomyelitis, 48 recovered or improved and 7 showed no effect. By "recovered or improved" it is meant that the wounds and sinuses healed completely while under treatment or the exudate was sterilized of staphylococci and the lesion was healing. In some cases the lesions have remained healed; in others they have recurred. The precise details and the number of recurrences will have to await the full reports of investigators and the passage of time, since no one who has had any experience with the treatment of acute and chronic osteomyelitis would be rash enough to make any final statements concerning the ultimate outcome of these cases until several years have passed.

One is justified in making the following statements: Following penicillin treatment the exudate decreases greatly in amount within a few days and organisms are quickly reduced in number. In a few cases the exudate obtained from the wounds is sterile within a period of a few days to a week and healing progresses rapidly, so that sinuses that have been present for months or years heal completely in two to three weeks.

Various routes of administration have been used, including constant intravenous injections, repeated intravenous or intramuscular injections and local treatment.

Empyema.—Seven of the 9 patients with staphylococcic empyema improved or recovered following penicillin treatment. One patient showed no effect and another patient died. The latter received only two injections into the pleural cavity, totaling only 28,000 units, and was only 3 weeks old.

In the patients who recovered or improved, it was possible to sterilize the pleural exudate over a period of several days by injecting between 40,000 and 50,000 Oxford units directly into the pleural cavity. It is important not to use penicillin as an irrigating solution, since it requires contact between the organism and the penicillin over a period of several hours for a maximum effect to take place. Even when the exudate is sterilized, it is often so thick that it is necessary to employ thoracotomy for adequate drainage. Once an empyema cavity is drained, it can be kept sterile by injecting penicillin into it daily. It has not been possible in the experience recorded to date to sterilize empyema cavities by the intramuscular or intravenous route.

As an aid in the treatment of staphylococcic empyema penicillin is one of the best remedies available.

Infections of the Skin and Subcutaneous Tissues.—In the discussion of staphylococcic infections of the skin and subcutaneous tissues with bacteremia it was pointed out that all 10 of the patients recovered. In this group of 23 patients 19 were greatly improved or recovered completely.

Of the patients who failed to show improvement, 1 had an abscess of the thigh, treated locally, 1 had extensive psoriasis with local staphylococcic infection of the lesions, 1 had a chronic ulcer of the skin and 1 had a chronic sinus of the skin, treated locally.

Of the 19 patients who recovered or improved, 7 received only local treatment varying from three to six days, with solutions of penicillin in concentration of 200 to 250 units per cubic centimeter on moist dressings. The total amount of penicillin used was small and varied from 2,000 to 25,000 Oxford units. The others received intravenous or intramuscular treatment for three to twenty-one days, and since most of them were over 50 years of age, with carbuncles or other serious infections, the results were impressive.

Parenteral and local treatment may be combined in many of these local infections, but parenteral injections for any but the most superficial lesions are to be preferred. Early and intensive treatment is also desirable.

Burns.—In the treatment of 9 patients with burns, penicillin was used intravenously and locally. Local applications were used in preparation for skin grafting in order to reduce the number of organisms or sterilize the surface. Parenteral treatment was employed to prevent invasive infections. In the 4 fatal cases the treatment was given for four to seven days for extensive burns of the body and extremities.

Fatal Cases.—The 11 deaths in this group were from empyema with pyopneumothorax (1 case), brain abscess (2 cases), burns (4 cases), multiple lung abscesses (1 case), reticulum cell carcinoma (1 case) and meningitis (2 cases). All these patients were desperately ill when penicillin was started, and in some the prognosis was definitely poor when one excluded the staphylococcic infection, such as the cases of extensive burns, the patient with the reticulum cell sarcoma and the patient with pyopneumothorax following resection of the esophagus.

STREPTOCOCCIC INFECTIONS OTHER THAN BACTERIAL ENDOCARDITIS

Thirty-three cases of streptococcic infections that were resistant to sulfonamide therapy were treated with penicillin. There were 23 due to the hemolytic streptococcus infections, 6 due to anaerobic streptococcus infections and 4 due to nonhemolytic streptococcus infections.

Hemolytic Streptococcus Infections.—In vitro studies show that hemolytic streptococci are more susceptible to the action of penicillin than is Staph. aureus. Of the 23 patients treated, 13 recovered or were greatly improved under treatment, 7 died, and no effect was observed in 3.

Two patients died following infections of the throat, with thrombophlebitis of the deep cervical veins (postanginal sepsis). Two patients had meningitis, 1 had cirrhosis of the liver and 1 had chronic nephritis. In the latter 2 cases the blood stream was sterilized but death followed from the primary disease. In the seventh case there was a large subphrenic abscess and a deep abscess of the muscles of the chest wall following a stab wound.

Of the 3 patients in whom no effect was observed, there were multiple ulcers of the skin associated with group C hemolytic streptococci in 1, another was a carrier, and a third had numerous ulcers of the skin due to the microaerophilic streptococcus.

Anaerobic Streptococcus Infections.—Of the 6 patients in this group 5 had anaerobic streptococcus infections of the uterus; 3 of these recovered and 2 died, 1 of a pulmonary embolus and the other of multiple abscesses of the lungs. The sixth patient had a skull fracture with meningitis and recovered.

Nonhemolytic Streptococcus Infections.—There were 3 deaths in this group and 1 patient showed no effect. Of the patients who died, 2 had a brain abscess, 1 of them with meningitis following a chronic empyema, and the third had multiple abscesses of the tissues. The patient who showed no improvement had pyelonephritis with endocarditis.

PNEUMOCOCCIC INFECTIONS

The pneumococcus is extremely sensitive to the action of penicillin. The results of treatment of 76 cases of pneumococcic infection are listed in table 2. Most of the cases of pneumonia were treated by Dr. W. S. Tillett, who will report his results in detail elsewhere. It is plain from the reported cases that penicillin is another potent weapon in the treatment of pneumococcic pneumonia, and many patients have recovered on less than 100,000 units given over a period of two to three days. Others have required more penicillin.

The results in the treatment of pneumococcic endocarditis were, on the whole, disappointing, although 1 patient treated under our direction recovered. The evidence for a bacterial endocarditis in this case was good, since an aortic insufficiency developed several days after bacteremia was detected, and the bacteremia persisted for several days after treatment was begun.

The results in the treatment of pneumococcic meningitis showed only 7 recoveries among 23 patients (30 per cent). In 2 the meningitis was accompanied by endocarditis. In many of the 16 fatal cases (70 per cent) the treatment was carried out with small doses given over a short period of time, and not all of them received penicillin intrathecally or intracisternally. Since Rammelkamp and Keefer [8] have reported that penicillin does not penetrate the subarachnoid space, and since the most striking results have been obtained in patients who received both intravenous and intrathecal treatment, there are good reasons for believing that better results will be obtained in the future, when patients are treated earlier in the course of the disease and when large amounts of penicillin are exhibited intravenously and intrathecally.

In the treatment of pneumococcic empyema the best results are obtained by injecting penicillin directly into the pleural cavity. Here sterilization of the exudate may be obtained, although the exudate may be reabsorbed very slowly. In some cases the process of reabsorption may be accelerated by aspiration or drainage of the cavity.

GONOCOCCIC INFECTIONS

The results of penicillin treatment of gonococcic infections have been extraordinarily good. Most of the 129 cases were treated by Dr. J. F. Mahoney and his asso-

TABLE 1.—*Summary of 500 Cases*

Diagnosis	No. of Cases	Recovery or Improvement	Death	No Effect
Staphylococcus aureus infections	228			
With bacteremia	91	54	34	3
Without bacteremia	137	109	11	17
Streptococcic infections	33			
Hemolytic streptococcus	23	13	7	3
Nonhemolytic streptococcus	4	0	3	1
Anaerobic streptococcus	6	4	2	..
Pneumococcic infections	76	45	29	2
Subacute bacterial endocarditis	17	3	4	10
Gonococcic infections	129	129	..	..
Meningococcic infections	5	4	1	..
Miscellaneous infections	12	5	3	4
Totals	500	306	94	40

ciates of the United States Public Health Service and are being reported by them. The results were satisfactory in 125 cases; that is to say, there was freedom from symptoms and they were bacteriologically negative within nine to forty-eight hours after treatment with between 100,000 and 160,000 units. The dosage varied from 10,000 units every three hours for sixteen doses to 20,000 units every three hours for five doses or 25,000 units every three hours for three doses. The precise details of treatment of these cases are being studied in order to define the minimum dosage and the so striking that only a few patients have been treated with penicillin. Five patients have been treated, with one death (20 per cent). The patient who died received no penicillin intrathecally. One patient who recovered received only parenteral therapy. The number of cases of meningococcic infection treated so far is so small that no definite conclusion can be drawn concerning the effectiveness of penicillin. The results are suggestive, however, that intravenous or intramuscular treatment is followed in some cases by recovery. It is likely that better results may be obtained by both parenteral and

TABLE 2.—*Detailed Summary of 500 Cases*

Diagnosis	No. of Cases	Recovery or Improvement	Death	No Effect
Staphylococcus aureus infection:				
With bacteremia:				
Sepsis without obvious port of entry	10	9	..	1
Acute osteomyelitis	22	18	2	2
Pyelonephritis	5	2	3	..
Infections of skin and subcutaneous tissues, including carbuncles, furuncles and cellulitis	10	10	..	..
Thrombophlebitis with or without pulmonary embolism	3	2	1	..
Burns	5	2	3	..
Pneumonia	5	3	2	..
Arthritis	1	1	..	..
Subarachnoid abscess	1	1	..	..
Meningitis	2	1	1	..
Cavernous sinus thrombosis	2	1	1	..
Postoperative wound infection	3	1	2	..
Epidural abscess	2	2	..	..
Orbital cellulitis	1	1	..	..
Endocarditis	9	..	9	..
Pansinusitis	1	..	1	..
Dissecting aneurysm of aorta	1	..	1	..
Cancer of rectum	1	..	1	..
Uremia from sulfadiazine	1	..	1	..
Aplastic anemia	2	..	2	..
Multiple abscesses	4	..	4	..
Totals	91	54	34	3
Without bacteremia:				
Osteomyelitis	55	48	..	7
Empyema	9	7	1	1
Postpartum sepsis	2	2	..	..
Infections of the skin and subcutaneous tissues	23	19	..	4
Laryngotracheitis	1	1	..	..
Brain abscess	3	1	2	..
Burns	9	5	4	..
Mastitis	5	5	..	..
Pneumonia	3	3	..	..
Lung abscess	3	2	1	..
Wound infection	1	1	..	..
Parotitis	1	1	..	..
Epidural abscess	1	1	..	..
Postoperative infection	4	3	..	1
Abscess, 1 case each (neck, abdominal wall, throat, right lower quadrant of abdomen, retroperitoneum, mouth, submentum, cheek, scalp)	9	6	..	3
Arthritis	1	1	..	..
Reticulum cell carcinoma	1	..	1	..
Meningitis	3	1	2	..
Prostatitis	2	2	..	..
Totals	137	109	11	16

Diagnosis	No. of Cases	Recovery or Improvement	Death	No Effect
Streptococcic infections other than bacterial endocarditis:				
Hemolytic streptococcus (23 cases):				
Postabortum sepsis	1	1	..	..
Bacteremia with meningitis	1	1	..	..
Conjunctivitis	1	1	..	..
Osteomyelitis of spine	2	2	..	..
Mastoiditis with bacteremia	1	1	..	..
Ulcer of skin	3	2	..	1
Microaerophilic ulcers of skin	1	..	..	1
Multiple abscesses of skin	1	1	..	..
Skin infection and subphrenic abscess	1	..	1	..
Empyema	2	2	..	..
Mastoiditis and pericarditis	1	1	..	..
Abscess of axilla	1	1	..	..
Post-tonsillitis sepsis	2	..	2	..
Cirrhosis of liver	1	..	1	..
Meningitis	2	..	2	..
Chronic nephritis	1	..	1	..
Carrier	1	..	..	1
Nonhemolytic streptococcus (4 cases):				
Pyelonephritis with endocarditis	1	..	..	1
Brain abscess	2	..	2	..
Multiple abscesses	1	..	1	..
Anaerobic streptococcus (6 cases):				
Septic abortion	5	3	2	..
Skull fracture, meningitis	1	1	..	..
Totals	33	17	12	4
Pneumococcic infections:				
Pneumonia	42	35	6	1
Meningitis	21	7	14	..
Meningitis with endocarditis	2	..	2	..
Endocarditis	6	1	5	..
Pericarditis	1	..	1	..
Pneumonia with empyema	3	2	1	1
Empyema	2	2	..	..
Totals	76	45	29	2
Gonococcic infections	129	129*	..	..
Meningococcic infections	5	4	1	..
Subacute bacterial endocarditis	17	3	4	10
Miscellaneous infections:				
Atypical pneumonia	1	..	..	1
Moniliasis	1	..	..	1
Agranulocytosis	1	1	..	..
Micrococcus tetragenus sepsis	1	1	..	..
Ulcerative colitis	1	1	..	..
Actinomycosis	3	1	2	..
Micrococcus aurantiacus sepsis	1	..	..	1
Escherichia coli—nonhemolytic streptococcus abscesses	1	..	..	1
Subscapular abscess—mixed infection	1	1	..	..
Putrid abscess	1	..	1	..
Totals	12	6	3	4

* Four of these cases showed only temporary improvement.

minimum time required to achieve the best results. It should be stressed that all these cases that responded to penicillin were those of sulfonamide resistant gonorrhea. Here, then, is a most potent weapon in the treatment of sulfonamide resistant gonorrhea, and it is not too much to predict that penicillin will prove to be one of the most effective agents in the treatment of a disease that causes great ineffectiveness in the armed forces and in the civilian population.

Meningococcic Infections.—The meningococcus, like the gonococcus, is extremely susceptible to the action of penicillin in vitro. The results of treatment of meningococcic meningitis with the sulfonamides have been intrathecal treatment. Additional experience is needed before any statements concerning the usefulness of penicillin in the treatment of these infections can be defined with assurance.

SUBACUTE BACTERIAL ENDOCARDITIS

At the beginning of this study our committee realized that the requests for penicillin for the treatment of subacute bacterial endocarditis would be numerous. We were anxious to give it a thorough trial in a limited number of cases in order to determine whether it was effective in controlling the infection. It was decided, therefore, that 10 cases would be thoroughly treated as

a pilot experiment, and if the results were not promising the experiments would be discontinued until larger amounts of penicillin became available. This policy was adopted because it was the opinion of the committee that the penicillin that was available should be conserved for the clinical investigation of cases of infection most likely to occur in wounded soldiers and sailors and in those infections in which penicillin was most effective.

Up to the present time 17 patients with bacterial endocarditis have been treated. There were 4 deaths (23 per cent). No appreciable effect on the course of the disease was noted in 10 of them (59 per cent). Three patients improved temporarily while under treatment, although 2 of these soon relapsed after treatment was discontinued. The amounts of penicillin used varied from 240,000 to 1,760,000 units over a period of from nine to twenty-six days. There is good evidence that some strains of organisms are slightly more susceptible to penicillin than others, and there is also evidence that the blood stream can be sterilized temporarily, at least in some cases. On the whole, however, the results in the few cases treated were disappointing. It is possible that some of these infections with susceptible strains of organisms may be influenced favorably if treatment is started early in the course of the disease and carried on in an intensive manner. This our committee hopes to be able to do when much larger amounts of penicillin become available for clinical investigation.

MISCELLANEOUS INFECTIONS

There were 12 cases of miscellaneous infections treated with penicillin. There was no effect in 1 case of atypical pneumonia, in 1 case of multiple subcutaneous abscesses due to Escherichia coli and nonhemolytic streptococci and in 1 case of moniliasis. Two patients with actinomycosis and 1 patient with a putrid abscess of the lung died. One patient with agranulocytosis and 1 with Micrococcus tetragenus sepsis recovered. One patient with ulcerative colitis was improved temporarily, and a patient with a mixed infection in a subscapular abscess improved following local use of penicillin.

GENERAL COMMENT

From the experience recorded so far, penicillin has been found to be extremely useful in the treatment of infections due to the staphylococcus, the hemolytic streptococcus, the pneumococcus and the gonococcus. It has been tested most extensively in the treatment of staphylococcic and gonococcic infections. The staphylococcic infections have included infections with and without bacteremia, acute and chronic osteomyelitis, cellulitis, carbuncles of the lip and face, suppurative arthritis, pneumonia, empyema, septic compound fractures, burns and epidural abscesses. It has been of great benefit in those cases of infection that are resistant to the sulfonamides. Experimentally it is a potent agent in gas bacillus infections, but up to the present time there are no studies on human cases. It has not been effective in the treatment of subacute bacterial endocarditis.

To obtain the best results it is necessary to inject penicillin continuously or at frequent intervals for at least seven to fourteen days or longer. This is necessary because penicillin is excreted rapidly in the urine and a large part of that injected is lost within a few hours. To keep organisms in infected areas exposed to the action of penicillin, then, it is essential that enough be given so that this objective is attained. Experience shows that the amount needed and the frequency of injection will vary from one patient to another and from one infection to another.

With respect to dosage the following schedule has been found useful in the various infections and for the present is the one that is being recommended by our committee. These suggestions are subject to change depending on individual circumstances and cases.

DOSAGE SCHEDULE IN VARIOUS INFECTIONS

A. *In Serious Infections Due to the Hemolytic Streptococcus, Staphylococcus Aureus or Pneumococcus, With or Without Bacteremia.*—An initial dose of 15,000 to 20,000 Oxford units should be given, with continuing dosage as follows:

1. Five thousand units every hour injected into the tubing of an inlying intravenous set or

2. Constant intravenous injection of a solution at a rate designed to deliver 5,000 to 10,000 units per hour. In a few cases it may be necessary to use larger doses.

3. After the temperature has returned to normal, the total dose in a twenty-four hour period may be reduced by half, but it should be continued for at least seven days after the temperature is normal.

TABLE 3.—*Reactions*

Type of Reaction	No. of Cases
1. Fever	5
2. Chills and fever	12
3. Thrombophlebitis at site of injection	19
4. Urticaria	14
5. Gluteal tenderness at site of injection	5
6. Headache, flushing of face	10
7. Tingling in testes	2
8. Pains in muscles	2

B. *In Chronically Infected Compound Injuries Such as Infected Compound Fractures or Septic Infections of the Soft Parts.*—An initial dose of 10,000 Oxford units should be followed by 10,000 units every two hours or 15,000 units every three hours parenterally, with local treatment as indicated. This schedule may have to be increased or decreased, depending on the seriousness of the infection and the response to treatment.

C. *Sulfonamide Resistant Gonorrhea.*—The minimum dosage schedule has not been worked out completely; 10,000 Oxford units every three hours intramuscularly or intravenously for twelve doses has been used with success. It is not unlikely that the same effect may be obtained with 20,000 units every three hours for five doses. The results of treatment should be controlled by culture of the exudate.

D. *Empyema — Streptococcic, Pneumococcic and Staphylococcic.* — Penicillin in isotonic solution of sodium chloride should be injected directly into the empyema cavity after aspiration of pus or fluid. This should be done once or twice daily, using 30,000 or 40,000 units, depending on the size of the cavity, the type of infection and the number of organisms. Penicillin solutions should not be used for irrigation. It requires at least six to eight hours for a maximum effect of penicillin, so that continuous action is needed.

E. *Meningitis — Staphylococcic, Pneumococcic and Streptococcic.*—Penicillin does not penetrate the subarachnoid space in appreciable amounts, so that it is

necessary to inject penicillin into the subarachnoid space or intracisternally in order to produce the desired effect. Ten thousand units diluted in isotonic solution of sodium chloride in a concentration of 1,000 units per cubic centimeter should be injected once or twice daily, depending on the clinical course and the presence of organisms. Intravenous or intramuscular injections should be carried on at the same time.

F. *Pneumonia.*—The dosage schedule for pneumococcic pneumonia has not been worked out satisfactorily, but for the present it is well to give between 60,000 and 90,000 units a day for three to seven days. Recovery has followed with smaller doses, but the foregoing schedule seems necessary, at least in some cases.

TOXICITY AND REACTIONS

One of the remarkable features of penicillin is its relatively low toxicity and the extremely low incidence of a systemic nature. This is all the more remarkable in view of the fact that the material that is available for clinical testing at present is perhaps not more than 10 to 15 per cent pure penicillin. The reactions observed in the 500 cases are listed in table 3.

Chills and Fever.—These were recorded in 12 cases and fever in 5. In several it was difficult to attribute these reactions to the penicillin, since chills and irregular fever were present before treatment was started and they continued for a short period following treatment. In others, however, it was plain that these reactions were definitely related to the injection of penicillin. This statement is supported by the observation that the injection of 10,000 units of penicillin from some lots caused chills and fever, whereas the injection of 5,000 units from the same lot caused no reaction. These reactions were transitory, and aside from the temporary discomfort to the patient they caused no difficulty. In a few patients who were afebrile before treatment was begun low grade fever varying from 100 to 101 F. would occasionally occur and last for several days. This was noticeable particularly in those patients who were receiving penicillin in large amounts continuously.

Urticaria.—Urticarial eruptions were reported in 14 cases. Their cause remains obscure, since in some of the cases the urticaria did not appear for several days after penicillin was discontinued, in others it did not recur when penicillin was again injected, and in still others it developed during the exhibition of it. Whether these reactions are due to some impurity in the penicillin cannot be stated at present. In several cases in which penicillin has been given after an attack of urticaria there have been no signs of recurrence. The urticaria usually disappears temporarily following the injection of epinephrine.

Thrombophlebitis.—This complication at the site of injection was recorded in 19 cases. It has been noted with certain lots of material and is likely to occur when injections are made repeatedly and when concentrated solutions are used. There is also some individual susceptibility to thrombophlebitis, since in several of the reported cases penicillin from the same lot injected into 1 patient would be followed by thrombophlebitis, whereas it would cause no reaction in a second patient. Pain along the course of the vein during the injection of material has been complained of by some patients.

Miscellaneous Complaints.—Transitory attacks of throbbing pain in the head, flushing of the face, tingling in the testes, pains in the muscles and constriction in the chest have been observed. All these complaints last only a few minutes and disappear spontaneously. It has been found that some impurity carried over from the extraction process used to remove pyrogens was responsible for these reactions. Passing the solutions through a Seitz filter removed the substances, and recent lots of penicillin have not caused these reactions.

Aside from the patients who developed urticaria, there have been none who have developed any signs of sensitivity to penicillin. A number of patients have received several prolonged courses of penicillin at varying intervals of time, and in none of them so far have any reactions been observed to a second or even a third course of treatment.

SUMMARY AND CONCLUSIONS

From the study of 500 cases of infection treated with penicillin the following conclusions are justified:

Penicillin is a remarkably potent antibacterial agent which can be given intravenously, intramuscularly or topically. It is ineffective when given by mouth.

Following intravenous or intramuscular injection it is excreted rapidly in the urine, so that in order to obtain an adequate amount of potent material in the circulating blood and tissues it is necessary to inject penicillin continuously or at frequent intervals; that is, every three to four hours.

Penicillin has been found to be most effective in the treatment of staphylococcic, gonococcic, pneumococcic and hemolytic streptococcus infections. It has been disappointing in the treatment of bacterial endocarditis. Its effect is particularly striking in sulfonamide resistant gonococcic infections.

While the dosage schedule requires additional investigation, it seems clear that the average patient requiring intravenous or intramuscular injections for serious staphylococcic infections requires a total of between 500,000 and 1,000,000 Oxford units, and the best results have been observed when treatment is continued for at least ten days to two weeks. At least 10,000 units should be given every two to three hours at the beginning of treatment, either by continuous intravenous injection or by interrupted intravenous or intramuscular injections.

Satisfactory results are obtained in sulfonamide resistant cases of gonorrhea following the injection of 100,000 to 160,000 units over a period of forty-eight hours.

Patients with pneumococcic pneumonia frequently recover following the use of 100,000 units given over a period of three days. This is especially important in sulfonamide resistant pneumococcic infections. It may be necessary to give between 60,000 and 90,000 Oxford units daily for four to seven days to get a maximum effect.

In the treatment of empyema or meningitis it is advisable to use penicillin topically by injecting it directly into the pleural cavity or the subarachnoid space.

Toxic effects are extremely rare. Occasional chills with fever, or headache and flushing of the face have been noted. Urticaria has been reported and thrombophlebitis at the site of injection has been described.

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MODIFIED PROTAMINE ZINC INSULIN: AN IMPROVEMENT ON STANDARD PROTAMINE ZINC INSULIN

COMPARATIVE STUDIES ON SIXTY-TWO DIABETIC PATIENTS

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The protamine zinc insulin now generally employed has proved valuable in the treatment of diabetes, but it has become increasingly evident that for many diabetic patients it is not ideal for maintenance therapy. This paper is the report of clinical investigations with a new form of modified protamine zinc insulin which has revealed distinct advantages in a series of 62 patients.

The use of the slow acting standard protamine zinc insulin has permitted a reduction in the number of injections necessary in the great majority of cases of diabetes. It has also diminished the wide fluctuations in the blood sugar occurring with several daily injections of regular insulin. It was hoped that good maintenance therapy in nearly all cases of diabetes could be established with a single daily injection of protamine zinc insulin. This hope has not been realized. In the six years since its introduction in February 1937 much has been learned about the degree of diabetic control possible with this form of modified insulin. When given once daily, protamine zinc insulin exerts a relatively constant effect on the blood sugar, operating in practically uniform degree throughout the twenty-four hours, but it does not have sufficiently rapid activity after injection to control the rise in blood sugar occurring after intake of food.[1] The time of injection of the daily dose of protamine zinc insulin and the relationship of the time of injection to meals have relatively little to do with the shape of the twenty-four hour blood sugar curve. The highest blood sugar values occur during the day after the intake of food, while the lowest levels are found during the fasting period of the night or early morning. In patients with mild diabetes requiring 40 units of insulin or less per day the rise in the blood sugar after meals may not be sufficient to be important. In many such cases a single dose of protamine zinc insulin daily establishes good control. When the diabetes is more severe, however, it is usually not possible to give enough protamine zinc insulin to prevent hyperglycemia after meals without causing hypoglycemia during the fasting hours of the night or early morning. Since a single injection of protamine zinc insulin may exert some effect for forty-eight hours or longer, the total amount of insulin acting at any one time is the sum of that being absorbed from two or three depots in which the precipitated material has been subcutaneously injected. The constant absorption of the insulin proceeds at the same rate during the night as during the day. In patients with severe diabetes the rise in the blood sugar level after meals is great and rapid. In the majority of such cases, if enough of the slowly absorbed protamine zinc insulin is given daily, hyperglycemia after food intake may be prevented, but the total insulin effect will be excessive with resultant hypoglycemia during the night. If the total daily carbohydrate allowance should be divided into six equal parts and the patient fed every four hours day and night, wide fluctuations in the blood sugar could be prevented. With this program, food absorption would be slower and more uniform to correspond with the slowly and uniformly absorbed insulin. Since such frequent feeding is not practical, an approach to it has been widely adopted, four meals a day being given instead of three, the last at 9 or 10 p. m. Small night meals, containing some protein and from 10 to 30 per cent of the day's carbohydrate, have made it possible to control the majority of patients with relatively mild diabetes with a single daily injection of protamine zinc insulin.

COMBINED THERAPY: A COMPROMISE

Diabetes that is moderate or severe, however, usually cannot be controlled with a single daily injection of protamine zinc insulin, even when a relatively large night feeding is employed. This problem has been met in a fairly satisfactory manner by ourselves and others [2] by giving a large dose of protamine zinc insulin and a smaller dose of regular or crystalline insulin in separate injections before breakfast daily. Thus the prolonged activity of protamine zinc insulin is utilized to prevent nocturnal hyperglycemia, while the regular insulin tends to control the rise in the blood sugar after meals. It is usually possible to adjust the dose of protamine zince insulin so that it will not be large enough to cause insulin reactions at night or so small as to permit nocturnal hyperglycemia. Although this method of "combined therapy," using both a slow acting insulin and a rapid acting insulin, works well in the great majority of relatively severe cases, two very serious objections can be brought against it: 1. It is a compromise method, still requiring two injections a day, even though both can be given before breakfast. One of the chief advantages of protamine zinc insulin is thereby partly nullified. 2. Combined therapy requires the manipulation by the patient of two very different forms of insulin, thus increasing the possibilities of error. One of the insulins is precipitated and must be mixed and for large doses is usually used in 80 unit strength; the other is clear, is given in smaller doses and is usually employed in 40 unit concentration. Therefore two different syringes with dissimilar calibrations are often necessary.

We have analyzed the histories of all the patients we followed and regarded as satisfactorily regulated during the three year period from Jan. 1, 1940 to Jan. 1, 1943. Patients who could not be brought under good maintenance control were not included in this group. Of the 219 patients who could be satisfactorily regulated 131 (60 per cent) needed only a single daily injection of protamine zinc insulin, while 88 (40 per cent) required combined treatment with separate injections of protamine zinc and regular insulin before breakfast daily. The average dose needed in the 131 cases controlled with protamine zinc insulin alone was 24 units. The average total daily insulin requirement of the

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88 cases needing combined treatment was 62 units. During the last half of the three year period we have become increasingly dissatisfied with the degree of control obtainable in severe diabetes with a single dose of protamine insulin daily. Of the last 154 cases (regulated in the past eighteen months) 81 (53 per cent) were maintained with protamine zinc insulin alone, while 73 (47 per cent) required combined therapy.

It is evident that treatment could be greatly simplified for a large proportion of diabetic patients if a form of insulin was devised which would, as the result of a single injection, exert an influence on the blood sugar similar to that exerted by a larger dose of protamine zinc insulin and a separate smaller injection of regular or crystalline insulin. This highly desirable insulin should have activity prolonged enough to control nocturnal hyperglycemia plus sufficient rapid activity to prevent excessive increase in the blood sugar following food intake during the day.

INVESTIGATIONS OF "INTERMEDIATE" INSULINS

A number of forms of modified insulin have been studied with the hope that one of them would prove to have just the proper proportion of prolonged to rapid activity, so that a single injection might take the place of the two separate injections now required for the great majority of patients with severe diabetes. Some of these modified insulins have shown characteristics more or less intermediate between those of market protamine zinc insulin and regular insulin. Among these are histone zinc insulin, clear (soluble or acid) protamine zinc insulin and globin insulin. A review of the clinical studies with these and the other forms of modified insulin so far investigated [3] reveals that, in general, market protamine zinc insulin gives better control throughout the twenty-four hours and is more predictable and reliable. We have recently completed a carefully controlled series of comparative studies,[4] with these conclusions: When compared on 18 patients, histone zinc insulin gave poorer diabetic control than that obtainable with market protamine zinc insulin. The desirable more rapid action was insufficient and there was less prolonged effect. Comparative studies on 11 patients with clear (acid) protamine zinc insulin revealed less satisfactory diabetic control than was secured with market protamine zinc insulin.

Since these forms of modified insulin were proving so disappointing, and because of the interesting observations of Wauchope [5] and of Ulrich,[6] we returned to the study of the modified protamine zinc insulins which can be prepared by combining protamine zinc insulin and regular insulin. In common with these and other workers we previously had found that, when the two forms of insulin are mixed in the proportions usually employed in separate injections in the combined method of therapy, all or practically all of the insulin is precipitated by the excess of protamine present. As a rule the doses of protamine zinc insulin utilized clinically when both types of insulin are employed are several times as large as the doses of regular insulin. Thus, when 45 units of protamine zinc insulin is mixed with 15 units of regular insulin the resultant insulin preparation actually contains 60 units of protamine zinc insulin. Ulrich, however, demonstrated that when regular or crystalline insulin is combined with equal or smaller amounts of protamine zinc insulin the resultant insulin preparations have unmistakably more rapid action than protamine zinc insulin. The results obtained by these workers and our own studies led us to conclude that, by combining various proportions of protamine zinc and regular insulin, modified insulins may be prepared with various degrees of intermediate activity. This concept was supported by assays performed in the laboratories of Eli Lilly & Co., since reported by Peck,[7] which revealed that, the larger the proportion of regular to protamine insulin used in preparing the modified insulin, the more prompt and intense and the less prolonged are the effects.

These premises were then adopted: 1. Since a graded scale of intermediate types of insulin can be produced by adding regular or crystalline insulin to standard protamine zinc insulin, the most widely applicable of such preparations should be selected for careful study. 2. Such a preparation should be standard and should not be varied from patient to patient, to keep the therapy of diabetes as simple as possible. 3. The desirable proportion of slow (protamine zinc) insulin effect to rapid (regular) insulin effect could be ascertained by determining the proportions found necessary to establish good control in those patients requiring combined therapy.

THE DESIRABLE PROPORTIONAL EFFECT

Eighty-eight of the 219 well regulated patients required combined therapy. The average ratio between the separately injected two forms of insulin was protamine zinc insulin 3 to regular insulin 1. More than 80 per cent of the patients were best controlled with a proportion between 2:1 and 4:1, and more than 60 per cent with a proportion between 2.5:1 and 3.5:1. It is interesting and important to note that Joslin [8] also found that a large proportion (more than 50 per cent of those on insulin therapy) of a recently analyzed series of diabetic patients required combined therapy and that the average doses needed were 39 units of protamine zinc insulin and 13 units of regular insulin. Here again the ratio required is 3:1. Our studies and those of other investigators indicated that an insulin having 3 parts slow action to 1 part rapid effect would be widely useful.

It was decided to prepare, if possible, an insulin having 75 per cent slow activity and 25 per cent rapid activity and to compare the control of diabetes obtainable with such a preparation with that secured with the forms of insulin therapy now generally employed.

PREPARATION AND CHARACTERISTICS OF THE SPECIALLY MODIFIED PROTAMINE ZINC INSULIN

It was found that several preparations with approximately the desired proportional effects could be made by mixing various amounts of protamine zinc insulin and regular insulin. The resultant proportions of soluble to precipitated insulin, and therefore the relative rapidity of action, depend on the excess of protamine present, the amounts of the two insulins used and the

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7. Peck, F. B.: Action of Insulins, Proc. Am. Diabetes A. 2: 67-83, 1942.

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p_H. Standard protamine zinc insulin contains an excess of about 40 per cent protamine zinc. Mixture of equal parts of the two insulins should therefore insure the combination of all this excess, leaving 60 per cent of the regular insulin (or 30 per cent of the total units in the mixture of equal parts) in soluble form. Centrifugation of such a mixture, however, reveals that all of the insulin is precipitated, since the p_H is close to 5, the isoelectric point of insulin, as the result of combining regular insulin (p_H 3) with protamine zinc insulin (p_H 7.2). Slight changes either to the acid or alkaline side of p_H 5 result in an unknown amount of the insulin returning to soluble form.

To avoid this uncertainty, and since an insulin with the p_H of body tissues seems desirable, equal parts of protamine zinc insulin and regular insulin were mixed with the p_H adjusted to 7.2. It was then found that an amount of soluble insulin closely approximating 25 per cent of the total insulin was present in the supernatant fluid after centrifugation. Chart 1 shows the effect of injection of the supernatant fluid from such a preparation made from 30 units of protamine zinc insulin and 30 units of regular insulin. The activity was in all respects similar to that exhibited by 15 units of regular insulin given to the same patient. Fifteen units of the special insulin preparation (25 per cent of the total 60 units) was in soluble form, while 45 units (75 per cent) was in the precipitate. Modified protamine zinc insulin so prepared was selected because of these desirable characteristics for comparative studies on patients with diabetes. After storage for many months its activity was unchanged, so it appears to be stable.

METHOD OF INVESTIGATION

Patients.—Diabetic patients were chosen for study who were not suffering from any complications which would disturb regulation of the blood sugar. Comparative observations with the various types of insulin therapy were made on 24 patients in the hospital, each patient remaining in the metabolism ward for several weeks. When it was found that good results were being obtained with the special modified protamine zinc insulin, investigation was started on office and clinic patients. Thirty-eight outpatients served as subjects for comparative observations. Patients with mild diabetes were included, but a special effort was made to include a large number of patients with the more severe grades of the disease, since the best test of the new insulin would be on these patients. A carefully weighed diet was given to the patients in the hospital, the diet for each patient being unchanged throughout the period of study. Likewise, no appreciable variation in the activity of each patient was permitted during the observations. The only factor altered from one period to another was the character of the insulin. Similar efforts were made to control the diet and activity of the outpatients. Regulation in the latter group is necessarily much less accurate than that obtained under the close supervision of the staff of the metabolism ward. However, the control secured in ambulatory outpatients engaged in their usual occupations will reflect more exactly the clinical usefulness of any form of insulin. The ages of the 62 patients ranged from 18 to 74 years, averaging 46 years.

Diets.—The diets used were those thought to be best for each patient, according to the individual age, size, nutritional status, activity and total caloric requirement. Protein allowances per day ranged from 56 to 110 Gm., fat from 30 to 180 Gm. and carbohydrate from 140 to 220 Gm. In nearly all cases a night feeding was given at 9:30 or 10 o'clock containing approximately 20 per cent of the carbohydrate, the remaining 80 per cent being divided equally among the three main meals. In certain cases, in which a definite indication was present, a somewhat larger proportion was given at lunch and supper. The average patient received 150 Gm. of carbohydrate daily, distributed as 40 Gm. each at breakfast, lunch and supper and 30 Gm. in the night feeding.

Insulins.—The special modified protamine zinc insulin was prepared for us in the laboratories of Eli Lilly & Co. It is made by admixture of equal parts of protamine zinc and regular insulin at p_H 7.2. The effect of the supernatant fluid (soluble insulin) by rabbit assay is approximately 10 units to each 30 units of precipitated insulin effect. For convenience and clarity in the remainder of this paper, this special modified protamine zinc insulin with 75 per cent slow effect and 25 per cent rapid effect will be referred to as 3:1 insulin. The Lilly Company has labeled this insulin for experimental purposes "Special Protamine Zinc Insulin" 40 or 80 units per cubic centimeter.

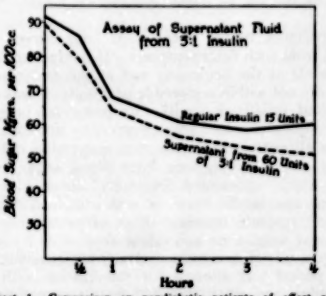

Chart 1.—Comparison on nondiabetic patients of effect of 15 units of regular insulin with that of the supernatant fluid from 60 units of the 3:1 modified protamine zinc insulin. The blood sugar curves are similar.

Comparative observations of the control of diabetes secured with 3:1 insulin with that obtainable with protamine zinc insulin alone, or when supplemented with regular insulin, were made in each case.

METABOLISM WARD STUDIES

Each patient was as carefully regulated as possible with diet and insulin. If the diabetes could not be controlled with a single daily dose of protamine zinc insulin, separate daily injections of protamine zinc insulin and regular insulin before breakfast were employed. Frequent blood sugar determinations were obtained, and careful quantitative urine sugar measurements were made in four separate periods daily: 7 to 11 a. m., 11 a. m. to 4 p. m., 4 to 9 p. m., and 9 p. m. to 7 a. m. Meals were given at 8 a. m., 12 noon and 5 p. m. Glycosuria was eliminated as completely as possible, and an effort was made to bring the blood sugar within normal limits. All conditions were then kept constant, including diet, activity and insulin dosage. If any complication appeared, such as fever, infection, change in activity, mistake in diet or unaccountable change in tolerance, the data were discarded. After at least four to seven days of relatively stable blood

sugar levels, twenty-four hour blood sugar curves were determined. Blood for sugar determinations was taken at 7:30 a. m. (fasting), 10:30 a. m., 2:30 p. m., 7:30 p. m., 12 midnight and again at 7:30 a. m. (fasting). The blood sugar values at 10:30 a. m., 2:30 p. m., 7:30 p. m. and at midnight each represent the level present two and one-half hours after the preceding meal. The constancy of these intervals lends meaning

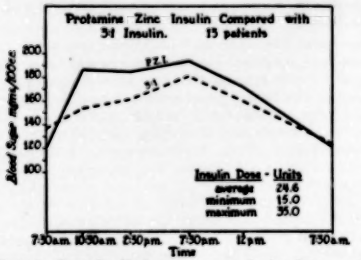

Chart 2.—Composite blood sugar curves showing better control of diabetes obtainable with the modified protamine zinc insulin.

and importance to the twenty-four hour curves constructed from such determinations. If the fasting blood sugar levels at the beginning and at the end of each curve were not within reasonable proximity, it was concluded that stabilization with that particular program was not satisfactory and such curves were not included.

When all criteria had been met, reasonable stability obtained and a twenty-four hour blood sugar curve secured which represented the control obtainable with protamine zinc insulin alone, or with combined therapy employing separate morning doses of protamine zinc and regular insulin, an equivalent dose of 3:1 insulin was begun, all other conditions being left constant. A similar period was allowed for stabilization with the 3:1 insulin, and when this had been accomplished a twenty-four hour curve was obtained reflecting the control obtained with the 3:1 modification.

RESULTS

1. *Standard Protamine Zinc Insulin Alone Compared with 3:1 Modified Protamine Zinc Insulin.*—Comparison of 13 patients studied in the hospital revealed better control in 10 of the cases throughout the twenty-four hours with 3:1 insulin than with standard protamine zinc insulin. In 2 cases the control was equally good with the two insulins, while in 1 case the standard protamine zinc insulin gave a better twenty-four hour curve. Statistical analysis of the individual figures obtained with the two insulins at 10:30 a. m. and 2:30 p. m., at which times the greatest differences occurred, show a probable significance favoring 3:1 insulin of 0.969.[9] At 10:30 a. m. the average of the blood sugar values obtained with 3:1 insulin was 23 mg. per hundred cubic centimeters lower than the average after standard protamine zinc insulin, and at 2:30 p. m. the average was 22 mg. lower. Blood sugar values were consistently lower with 3:1 insulin throughout the day and at midnight, but the level of the fasting blood sugars was slightly higher (table 1). The characteristics exhibited by the new insulin modification are desirable. The soluble insulin content resulted in somewhat lower blood sugars during the day after the intake of food. The fasting blood sugars were the same or slightly higher, showing that the fasting period during the night is adequately controlled, while there is less tendency to produce hypoglycemia than occurs with standard protamine zinc insulin. The 3:1 insulin did not produce a single instance of nocturnal hypoglycemia. The equal doses of standard protamine zinc insulin and of 3:1 insulin which were compared were 35 units in 3 instances, 30 units in 3 cases, 25 units twice and 15 units 5 times. The average dose was 24.6 units. Not only was there less variation in the blood sugar levels throughout the day with 3:1 insulin but the total insulin effect was greater. It seemed to be more effective unit for unit than standard protamine zinc insulin. No doubt this resulted from the fact that there was less fluctuation of the blood sugar, and less of the insulin effect was spent in bringing back an abnormally high blood sugar value toward normal. Similarly, fewer units per day are needed with standard protamine zinc insulin than are necessary with multiple injections of regular insulin, because of the greater relative stability of the blood sugar. Composite comparative curves have been constructed from the mean values of the blood sugar determinations secured throughout the twenty-four hours with standard protamine zinc insulin and with 3:1 insulin (chart 2). In this group of cases the 3:1 insulin gave definitely superior regulation.

2. *Combined Therapy Compared with 3:1 Modified Protamine Zinc Insulin.*—The control secured with separate injections of protamine zinc insulin and regular insulin should theoretically be identical with that obtainable with the 3:1 modified protamine zinc insulin if the proportions of the protamine zinc insulin and regular insulin are 3 to 1. Although the average doses used for the 11 patients in the hospital were 45 units of protamine zinc insulin and 13 units of regular insulin (ratio 2.9:1), the individual doses employed ranged from 60 and 10 (6:1) to 35 and 15 (2.3:1). Table 2 shows the blood sugar values obtained throughout the

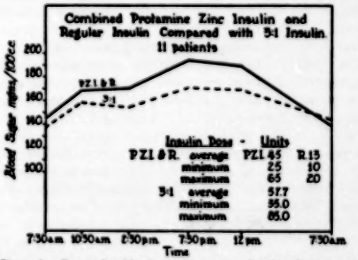

Chart 3.—Composite blood sugar curves showing better control of diabetes obtainable with the modified protamine zinc insulin than with "combined therapy."

twenty-four hours with separate doses of protamine zinc and regular insulin as compared with those obtained with 3:1 insulin, the doses of the latter being equal to the combined number of units used with the two separate injections. In 7 of the 11 cases the regulation was better with 3:1 insulin, in 3 instances the control was better with combined therapy and in 1 instance the effects were approximately equal. The composite curves (chart 3) show similar contours, illustrating that the

9. The statistical analyses were done according to Fisher's formula. A result of 0.95 or greater indicates significance in the statistical sense which could not be due to error in random sampling.

desired effect of securing from a single injection results like those following separate injections of the two different insulins has been obtained. The fact that 3:1 insulin gave even better control, with somewhat lower blood sugars and less glycosuria throughout the twenty-four hours in the majority of cases, was somewhat unexpected. No doubt this can be explained by the greater uniformity of the insulin action and by the fact that the 3:1 proportion actually met the needs of the patients better than the various proportions individually employed in the combined therapy. Statistically the probable significance favoring the 3:1 insulin was 0.958.

TABLE 1.—*Protamine Zinc Insulin Compared with 3:1 Insulin*

Case	Insulin	Units	7:30	10:30	2:30	7:30	12	7:30
1	PZI	15	157	205	219	218	200	161
	3:1	15	153	208	221	204	191	162
2	PZI	15	134	181	240	201	196	141
	3:1	15	154	176	210	208	192	185
3	PZI	15	80	175	214	213	150	105
	3:1	15	107	112	166	220	166	107
4	PZI	15	165	205	215	176	197	135
	3:1	15	117	224	220	188	117	144
5	PZI	15	99	150	145	162	150	122
	3:1	15	119	122	136	114	140	139
6	PZI	35	157	220	196	217	164	137
	3:1	35	120	197	140	228	137	132
7	PZI	30	79	180	208	209	211	100
	3:1	30	91	101	164	184	175	123
8	PZI	35	95	150	121	105	81	63
	3:1	35	143	155	150	209	132	111
9	PZI	35	150	220	178	225	...	157
	3:1	35	126	155	143	169	175	119
10	PZI	30	153	220	210	164	209	139
	3:1	30	...	156	143	96	144	89
11	PZI	25	137	235	214	237	221	160
	3:1	25	123	157	197	122	162	160
12	PZI	25	66	99	137	130	86	60
	3:1	25	74	160	135	191	141	94
13	PZI	30	146	150	113	148	162	92
	3:1	30	126	87	85	166	175	116

OUTPATIENT STUDIES

The hospital studies, which were performed first, showed that it would be safe to change outpatients from the usual forms of regulation to 3:1 modified protamine zinc regulation if the fact was kept in mind that the 3:1 insulin is somewhat more effective unit for unit. It had also been learned that the 3:1 insulin could be used in relatively large doses, 85 units for example, being substituted for amounts as great as protamine zinc insulin 65 units and regular insulin 20 units (cases 1 and 5, table 2). It was evident that the most important test of the new insulin would occur when it was used instead of the usual forms of insulin treatment for patients requiring large doses and engaged in their normal occupations. Comparative studies were done on 38 outpatients who were housewives, business men, mechanics, laborers and students ranging in age from 18 to 62. Quantitative urine sugar determinations were not possible in the outpatient group. Patients were instructed to record fasting, late morning and before supper urine tests as negative or 1 to 4 plus qualitative Benedict's reactions. In each case the best possible regulation was first secured with standard protamine zinc insulin alone, or with protamine zinc and regular insulin in separate daily injections before breakfast. After at least one week of relatively stable conditions, as illustrated by the patient's urine test record, blood for sugar determination was taken fasting and again two and one-half hours after the patient's usual breakfast. Then 3:1 insulin was substituted for the previous form of insulin, the diet and all other conditions being kept as constant as possible. After a week the urine tests were compared with those obtained on the previous program, and sugar determinations were done on the fasting blood and that obtained two and one-half hours after exactly the same breakfast.

RESULTS

1. *Standard Protamine Zinc Insulin Alone Compared with 3:1 Modified Protamine Zinc Insulin.*—Comparison of these two forms of insulin in equal doses on 8 outpatients revealed better regulation with the new insulin modification in all cases, as shown by decreased glycosuria, less tendency to high blood sugar values after breakfast and less fluctuation in control. The fasting blood sugar levels were somewhat higher in 6 of the 8 cases, showing the less prolonged action of 3:1 insulin. The blood sugar values after breakfast were lower in every case when 3:1 insulin was used, illustrating the desirable more rapid effect. The average blood sugar rise after standard protamine zinc insulin when determined two and one-half hours after breakfast was 81 mg., while that after 3:1 insulin was only 16 mg. per hundred cubic centimeters (table 3).

2. *Combined Therapy Compared with 3:1 Modified Protamine Zinc Insulin.*—Thirty outpatients were studied in this group, and in 26 of the 30 cases control obtained with 3:1 insulin was as good as or better than that secured with separate injections of protamine zinc insulin and regular insulin. In 4 patients the control was somewhat better with standard protamine zinc insulin. Theoretically the control should be identical if the proportion used in the combined therapy was exactly 3:1 and if the same doses of 3:1 insulin were used as the total employed in each case in the combined therapy. The doses employed were not exactly the same. Somewhat smaller doses of 3:1 insulin were used in some cases because of its greater effectiveness per unit. In the cases requiring 80 or more units total under the combined treatment, amounts from 5 to 15 units less were employed when the change was made to 3:1 insulin. There were 10 such cases among the 30, from 70 to 75 units of 3:1 insulin being substituted for from 80 to 95 units of total insulin in the combined treatment, according to individual indications. The 30 patients selected for this comparative

TABLE 2.—*Combined Therapy Compared with 3:1 Insulin Control*

Case	Insulin	Units	7:30	10:30	2:30	7:30	12	7:30
1	PZI 60 & R	20	150	191	197	218	220	115
	3:1	85	123	99	167	140	165	169
2	PZI 60 & R	10	81	117	156	194	261	149
	3:1	70	61	145	135	134	179	116
3	PZI 35 & R	10	128	167	95	144	119	109
	3:1	35	142	155	128	209	132	111
4	PZI 35 & R	10	157	148	155	148	119	135
	3:1	35	151	117	87	150	155	127
5	PZI 60 & R	25	150	205	205	213	211	147
	3:1	85	113	164	...	210	160	97
6	PZI 60 & R	10	211	274	241	205	251	216
	3:1	80	197	249	222	242	230	212
7	PZI 35 & R	15	127	161	161	221	160	120
	3:1	80	88	87	144	151	155	88
8	PZI 60 & R	10	141	84	116	102	170	112
	3:1	70	108	138	123	104	138	131
9	PZI 35 & R	10	75	70	151	184	128	64
	3:1	45	135	202	102	74	184	174
10	PZI 30 & R	10	96	91	131	193	200	129
	3:1	40	130	178	147	204	233	160
11	PZI 60 & R	10	257	203	219	240	213	246
	3:1	70	213	204	166	176	183	181

study had the most severe diabetes under good regulation we have observed. Their cooperation was secured largely through the hope that one injection of the new insulin might be substituted for the two morning injections which all of them had needed.

The average dose of protamine zinc insulin required in the 30 cases was 51.3 units (range 30 to 70), and the average regular insulin needed was 16.6 units (range 10 to 25). The average ratio in this group was 3.1:1, corresponding closely with the average ratios in all our other groups of patients requiring combined therapy. The range of the ratios between the two forms of insulin required was 4.5:1 to 2.8:1. The average total protamine zinc insulin plus regular insulin requirement was 67.9 units (ranging from 40 to 95 units), while the average dose of 3:1 insulin substituted for the combined therapy was 65.6 units (ranging from 40 to 95 units). In spite of the fact that somewhat smaller doses were used in one third of the cases, the 3:1 insulin control was better than that obtained with combined treatment in 13 of the 30 cases, just as good in another 13 cases and less effective in only 4 instances. With the combined treatment the average blood sugar level two and one-half hours after breakfast was only 28 mg. per hundred cubic centimeters higher than the fasting level, indicating good control. With the 3:1 insulin, however, the rapid part of the insulin action was even more effective, since the average 10:30 a. m. blood sugar value was only 18 mg. per hundred cubic centimeters higher than the average fasting blood sugar level. The fasting blood sugar values were satisfactory with both types of insulin therapy, averaging almost exactly the same, 139 mg. The blood sugar values in individual instances were very close also at 10:30 a. m., averaging 9.5 mg. per hundred cubic centimeters lower with 3:1 insulin than with the combined treatment (table 4).

TABLE 3.—*Protamine Zinc Insulin Compared with 3:1 Insulin on Eight Outpatients*

Insulin	Average Dose, Units	Average Blood Sugars 7:30 A. M. (Fasting)	Mg. per 100 Cc. 10:30 A. M. (2½ Hours After Eating)
PZI	39	121	202
3:1	39	129	147

TABLE 4.—*Protamine Zinc Insulin and Regular Insulin Regulation (Combined Therapy) Compared with 3:1 Insulin Control on Thirty Outpatients*

Insulin	Average Dose, Units	Average Blood Sugars 7:30 A. M. (Fasting)	Mg. per 100 Cc. 10:30 A. M. (2½ Hours After Eating)
PZI & R	67.9	139.2	167
3:1	65.5	139	157.5

COMMENT

The better regulation secured with the special form of modified protamine zinc insulin having 75 per cent slow effect and 25 per cent rapid effect can be explained by the fact that the characteristics of this insulin are designed to meet the requirements of a large proportion of diabetic patients. It seemed likely that this insulin, prepared especially for patients with severe diabetes requiring separate daily doses of protamine zinc insulin and regular insulin, would produce effects similar to those produced by the combined therapy. As shown by these studies, the results were similar, a single dose of the 3:1 insulin not only giving control as good as that obtained by combined therapy but giving better regulation in most cases.

Less expected were the better effects of 3:1 insulin when compared with protamine zinc insulin regulation alone in milder diabetes. Decreased glycosuria and more stable blood sugar resulted in most of these cases. In no case was hypoglycemia observed. Hypoglycemia might have occurred had the rapid effect of the 3:1 insulin been excessive and would probably have been evident as low 10:30 a. m. blood sugar values. No such tendency was detected. Even when patients had been relatively well controlled with small doses of protamine zinc insulin the use of 3:1 insulin usually improved the regulation. Thus of the 5 cases requiring 15 units each in table 1 (cases 1 through 5) 3 showed better control with 3:1 insulin, while in the other 2 the control was as good as that obtained with standard protamine zinc insulin. The rapid insulin effect of 3:1 insulin in the 15 unit dose is 25 per cent of 15, or 3.75 units. When the 3:1 insulin was substituted for larger doses of protamine zinc insulin, the rapid insulin effect increased proportionately. For example, patients requiring 40 units got approximately 30 units slow effect and 10 units rapid effect, which for most patients seemed to be a convenient proportion and improved the regulation.

Colwell, Izzo and Stryker [3] have obtained encouraging results with an insulin modification made by mixing 2 parts of crystalline insulin with 1 part of protamine zinc insulin, without readjustment of the p_H. In such a preparation all of the insulin is precipitated, but the activity is more rapid than that of protamine zinc insulin. Changes in the p_H, however, result in considerable alteration in the amount of soluble insulin which may be released in such a mixture. If mixed at p_H 7.2, for example, 50 per cent of the total insulin present is released in the soluble, quickly absorbable form. Since the p_H of the body tissues is approximately 7.2, there would seem to be danger of sudden absorption of a large amount of rapid acting insulin, with resultant hypoglycemia. We have observed this in a few patients treated with such a preparation. It seems safer to use 3:1 insulin, with the known p_H of 7.2, which is unchanged after injection. With 3:1 insulin the proportion of the precipitated to the soluble insulin is the same in the insulin vial as the proportion of the physiologic activities of the precipitated and soluble fractions after injection.

CLINICAL REGULATION SIMPLIFIED

To be of value clinically, a new insulin modification should not complicate the regulation of diabetes and should if possible simplify it. Treatment was greatly simplified in 34 of the 41 cases on combined therapy, since in these cases previously requiring two injections daily it was possible to substitute one injection of the modified 3:1 protamine zinc insulin. Clinical regulation is carried out as with standard protamine zinc insulin. The presence or absence of glycosuria before breakfast and before lunch and supper gives the most information. When combined therapy is used the absence of early morning glycosuria usually means that enough or too much protamine zinc insulin is being given. Glycosuria before breakfast usually suggests the need for an increase in the protamine zinc insulin dose. Absence of glycosuria before lunch and supper usually means that enough or too much regular insulin is being used. Glycosuria during the day requires an increase

in the regular insulin dose. With the specially modified 3:1 protamine zinc insulin, however, the fasting and postprandial urine tests are apt to change together rather than separately. When the amount of 3:1 insulin given is sufficient to prevent glycosuria at night there is apt to be little or no glycosuria during the day because of the proportional rapid insulin effect. Whenever glycosuria occurs during one part of the day while there is no sugar in the urine during most of the day, a slight change in the distribution of the carbohydrate allowance will usually suffice to reduce or abolish the glycosuria.

The 3:1 modified protamine zinc insulin was substituted with advantage both in cases requiring relatively small doses of insulin (usually protamine zinc insulin alone) and in cases requiring large doses of insulin (usually separate injections of protamine zinc insulin and regular insulin). Among the total of 62 patients there were 20 requiring 40 units or less of insulin daily, 14 requiring from 40 to 60, 18 from 60 to 80 and 10 from 80 to 95 units. Better control was obtained in all these groups with 3:1 modified protamine zinc insulin than with the usual methods of insulin regulation.

SUMMARY

A study covering three years and including 219 well controlled cases showed that a single injection of protamine zinc insulin as a rule established good regulation only in mild diabetes. The successful regulation of moderate or severe diabetes usually required separate daily injections of protamine zinc insulin and regular insulin ("combined therapy"). The proportion most widely useful was 3 parts protamine zinc insulin to 1 part regular insulin. Therefore a modified protamine zinc insulin with 3 parts prolonged action to 1 part rapid action was prepared. It is made by admixture of equal parts of protamine zinc insulin and regular insulin at p_H 7.2. Comparative studies of the new insulin were done on 62 patients. These showed that a single injection of this 3:1 insulin modification gave a good control or better control than that obtained with combined therapy in 34 of 41 cases. In 20 of 21 milder cases the new insulin modification gave results as good as or better than those secured with a daily injection of protamine zinc insulin.

CONCLUSIONS

1. A modified protamine zinc insulin having 75 per cent slow or precipitated insulin effect to 25 per cent rapid or soluble insulin effect can be substituted with advantage for the forms of insulin now employed in maintenance therapy of diabetes. Since the effects of this insulin are more closely adjusted to the requirements of most patients with diabetes, better control is possible with it than with standard protamine zinc insulin. A single injection daily should permit good regulation in the great majority of cases.

2. The use of multiple forms of insulin should be discouraged. Good therapy of diabetes requires simplicity. Two forms of insulin should be sufficient: (*a*) A modified protamine zinc insulin such as that used in these studies. Such a modified insulin might well be substituted for the standard protamine zinc insulin now used, because of the better results in controlling uncomplicated diabetes. (*b*) Regular (or crystalline) insulin, for use in diabetic emergencies and whenever supplementary insulin is required.

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PROTAMINE ZINC INSULIN MODIFIED FOR ACCELERATED ACTION

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In the routine treatment of diabetes mellitus it is often necessary to use simultaneously two types of insulin with different timing and intensity qualities of action. Protamine zinc insulin with its desirable slow, weak and prolonged effects must often be supplemented by separate injection of soluble insulin with its equally desirable prompt, intense and brief effects.[1] The separate use of these two types is often necessary in severe diabetes because protamine zinc insulin in dosage low enough to avoid hypoglycemia between meals or at night usually permits glycosuria after meals. Supplementary injection of insulin in solution, either "regular" (amorphous) insulin or solution of zinc insulin crystals, helps to control postprandial glycosuria and is less likely to cause insulin shock during sleep because of its brief action. In small amounts it cannot be mixed with protamine zinc insulin because it is precipitated with loss of prompt effectiveness.

The use of two insulins simultaneously is confusing and involves multiple subcutaneous injections. It is necessary because the prolonged timing and intensity characteristics of protamine zinc insulin were not analyzed carefully enough in the course of its commercial development. Modification of it into an ideal preparation for daily use is a simple matter. In such an improved form therapeutic results are far more satisfactory than with orthodox methods. The reasons for this point of view are the subject of the present report. In preface it may be profitable to review some of the important factors leading to the development of protamine zinc insulin in its present commercial form.

PROTAMINE ZINC INSULIN

Composition.—Hagedorn's[2] original selection of a protamine to precipitate insulin into a suspension suitable for depot injection was based on the presumption that the greater its insolubility the more useful it would be in treatment. Therefore he chose a protamine which, when precipitated by insulin, is least soluble at the hydrogen ion concentration of human serum of all the protamines studied.

Proportions of insulin and protamine were selected which would yield complete precipitation of insulin at the point of least solubility of the compound. In fact an excess of protamine was and is used to insure maximum insolubility. This excess may vary somewhat in the products of different manufacturers. American products contain about double the amount necessary for complete precipitation when buffered to a p_H of 7.2 to 7.3 or from 0.75 to 1.25 mg. per hundred units of insulin.[3] Thus a preparation of greatest possible insolubility is formed, which releases insulin for one to three days from a single depot.

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2. Hagedorn, H. C.; Jensen, B. N.; Krarup, N. B., and Wodstrup, I.: Protamine Insulinate, J. A. M. A. **106**: 177-180 (Jan. 18) 1936.

3. Protamine Zinc Insulin, U-40, New and Nonofficial Remedies, 1941, p. 293.

The addition of zinc to protamine insulin, used primarily for the purpose of increasing its stability and preventing cohesion of the precipitate in heat, prolongs its action still further. As shown by Scott and Fisher and others,[4] zinc and other heavy metals possess the property of prolonging the effect of any insulin mixture. Thus protamine insulin, originally designed for maximum insolubility, was made even more insoluble with zinc, its present marketed form containing about 0.2 mg. of zinc per hundred units.[5]

Therapeutic Virtues and Faults.—The practical application of such a suspension in diabetic therapy certainly involves many advantages. By its use multiple injections are reduced, glycosuria is better controlled on the average, violent insulin shock is less frequent, acidosis is less likely to occur, and general health and nutrition in severe diabetes are improved.[5] Yet experience reveals certain well defined disadvantages inherent in a preparation of such insolubility, all due to slow or uncertain absorption.

Because of its slow, weak and prolonged effect extending over a period of several days, daily depots yield a continuous

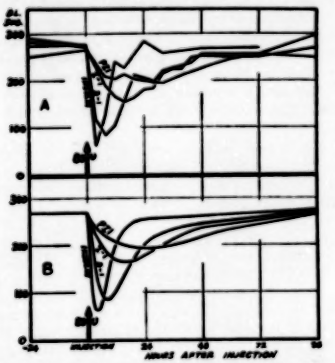

Chart 1.—Variable timing and intensity characteristics of soluble (regular) insulin, insoluble (protamine zinc) insulin, and modifications of protamine zinc insulin containing less protamine in proportion to the insulin. The lower series of curves are arbitrarily smoothed replicas of the actual curves shown above. The modification marked 2-1 is the one chosen for therapeutic trial in the group of 60 cases reported.

supply of insulin at undulating basic levels characteristic of the individual and dosage. Two difficulties arise from this source:

First, the continuous supply fails to allow for intermittent feeding and fasting habits, so that glycosuria tends to follow meals and hypoglycemia tends to appear during fasting, particularly at night or if the morning meal is delayed.[6]

Supplementary injection of soluble insulin partially corrects these faults, but multiple injections again are involved, the very thing that protamine zinc insulin was designed to avoid. Small supplementary doses of soluble insulin are ineffective if mixed with larger amounts of protamine zinc insulin because the excess of protamine in the latter immediately precipitates insulin added to it, thus increasing the dose of protamine zinc insulin by the amount of insulin added.[7]

Second, even though the dosage is constant, the action is often unpredictably variable. Probably because of variations in rates of absorption from different depots, unexpected waves of glycosuria or hypoglycemia tend to appear, causing an undulating type of control in spite of constant conditions of therapy.[8] Because these irregularities are unpredictable, they are not manageable by supplementary injections of soluble insulin. Too often they magnify the characteristic action of protamine zinc insulin; i. e., nocturnal fasting hypoglycemia or postprandial glycosuria.

MODIFICATION OF PROTAMINE ZINC INSULIN

Both in Denmark and in this country early investigators had insight into these timing factors. Most of the preliminary studies by Hagedorn and his colleagues were made with preparations containing no added zinc but excesses of protamine. Even when injected twice a day in efforts to adjust to feeding and fasting, these slightly less insoluble preparations permitted greater reduction of sugar during the night and poorer control after meals.[2] Appreciating their probable disadvantages, Krarup[9] reported a single experiment with insulin 341 "the effect of which is both quick and of long duration. It is prepared so as to contain in the same volume twice as many units of insulin as are ordinarily used." This was the first reported action of a protamine mixture with intermediate action comparable to that of similar modifications to be reported.

Root, White, Marble and Stotz[10] also pointed out that "it would be advantageous to have an insulin preparation—perhaps a slightly less insoluble protamine insulinate than the one now used—the action of which combines the desirable effects of both the 'old' and the 'new' insulin. Dr. Hagedorn writes that active work along this line is being continued in his laboratory."

These early suggestions have been followed up by Ulrich using mixtures containing 3 parts of soluble insulin and 2 parts of protamine zinc insulin,[11] and by ourselves using greater excesses of soluble insulin.[12] It is possible to modify the action of commercial protamine zinc insulin by the addition to it of excesses of soluble insulin. Its action is thereby accelerated to the extent that daily morning injections yield more insulin when needed during the feeding period of the day and less at night during fasting. Because such modifications are more soluble than standard protamine zinc insulin they also are somewhat more uniform in the effect of repeated single injections, although not so much so as soluble insulin. Thereby unpredictable variations in consistency of control are reduced and clinical usefulness is improved. Composite blood sugar curves in stabilized diabetic patients illustrating the action of single doses of protamine zinc insulin, soluble insulin and two intermediate mixtures of the two containing excesses of the latter are shown in chart 1.

Comparison of Mixtures Made with Crystalline and Regular Insulin.—Subsequent study of intermediate preparations confirms the essential timing and intensity properties previously reported for such modifications in many cases. Because of its eight to sixteen hour peak

4. Scott, D. A., and Fisher, A. M.: Studies on Insulin with Protamine, J. Pharmacol. & Exper. Therap. **58**: 78-92 (Sept.) 1936. Kerr, R. B.; Best, C. H.; Campbell, W. R., and Fletcher, A. A.: Protamine Insulin, Canad. M. A. J. **34**: 400-401 (April) 1936. Rabinowitch, I. M.; Foster, J. S.; Fowler, A. F., and Corcoran, A. C.: Clinical Experiences with Protamine Zinc Insulin and Other Mixtures of Zinc and Insulin in Diabetes Mellitus, ibid. **35**: 239-252 (Sept.) 1936.

5. Joslin, E. P.: Protamine Insulin and Its Advantages, New England J. Med. **215**: 1166-1168 (Dec. 17) 1936.

6. Joslin, E. P.: Difficulties in the Use of Protamine Zinc Insulin, J. A. M. A. **110**: 90-91 (Jan. 8) 1938.

7. Sprague, R. G.; Blum, B. B.; Osterberg, A. E.; Kepler, E. J., and Wilder, R. M.: Clinical Observations with Insulin Protamine Compound, J. A. M. A. **100**: 1701-1705 (May 16) 1936. Masters, T. D.: The Use of the Newer Insulins, Illinois M. J. **78**: 319-323 (Oct.) 1940.

8. Kepler, E. J.: Clinical Experience with Protamine Zinc Insulin, J. A. M. A. **110**: 92-96 (Jan. 8) 1938.

9. Krarup, H. B.: Clinical Investigations into the Action of Protamine Insulinate, Copenhagen, G. E. C. Gad, 1935, p. 52.

10. Root, H. F.; White, Priscilla; Marble, Alexander, and Stotz, E. H.: Clinical Experience with Protamine Insulinate, J. A. M. A. **106**: 180-183 (Jan. 18) 1936.

11. Ulrich, Helmuth: Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulins, Ann. Int. Med. **14**: 1166-1179 (Jan.) 1941.

12. Colwell, A. R.; Izzo, J. L., and Stryker, W. A.: Intermediate Action of Mixtures of Soluble Insulin and Protamine Zinc Insulin, Arch. Int. Med. **69**: 1-21 (June) 1942.

action and satisfactory twenty-four hour intensity, the modification made by mixing 2 parts of soluble and 1 part of protamine zinc insulin (2 to 1 mixture) was selected for detailed study and therapeutic trial.

The curves shown in chart 2 illustrate the response of the blood sugar concentration to single doses of two variations of this modification. Three patients with mild diabetes were fed every four hours night and day. Meals of approximately equal value eventually led to relatively constant high preabsorptive blood sugar levels. When such constancy was established, single injections of the insulin to be tested were given and the blood sugar was determined every four hours until the effects waned.

Twelve observations were made with mixtures containing 2 parts of regular insulin and 1 part of protamine zinc insulin. These responses were compared with sixteen other observations of mixtures containing 2 parts of solution of zinc insulin crystals and 1 part of protamine zinc insulin. Both preparations were used in the U-80 strength only, and all ingredients were products of the same manufacturer.[13] Previous study has demonstrated the stability of such modifications when mixed in the ampule prior to injection,[12] so all mixtures were prepared in that manner. The first three sets of curves represent averages for two to six responses to identical doses of the same preparation in the same patient.

Because of slight variations in control levels, all values were calculated in percentage of control levels for each modification and are averaged as shown in the lowest curve.

The results show a slight but measurable difference in the intensity of the two preparations containing the same proportions of soluble and protamine zinc insulin. Those made with regular insulin were slightly more prompt and 10 to 20 per cent more intense eight to sixteen hours after injection than those made with crystalline insulin. A measurable difference does not appear at twenty-four hours or thereafter. Judging from other unreported studies, the preparation made with 2 parts of regular insulin appears to resemble one containing about 2½ parts of crystalline insulin and 1 part of protamine zinc insulin.

This slightly more intense peak action of mixtures made from regular insulin can be explained on the basis of its content of inert protein, as suggested by Peck.[14] "Regular" or amorphous insulin yields only about 22 units per milligram on assay compared with 26 units per milligram from purified crystalline products. This is because amorphous insulin contains 10 to 20 per cent inert protein not contained in crystalline insulin. Protamine is a general protein precipitant. Therefore part of the excess protamine entering amorphous insulin mixtures precipitates the small fraction of inert protein, thus reducing the amount of protamine available for insulin precipitation. The net result is more soluble insulin and more intense action than in mixtures made with recrystallized insulin, in which all available excess protamine precipitates insulin, slowing and weakening the action of the mixture.

This difference is probably not of much practical importance. We have used both modifications in clinical therapy, frequently comparing their effects by transfer from one to the other in the same patient. With the regular 2 to 1 preparation there is a slightly greater tendency to afternoon hypoglycemia than with the crystalline 2 to 1 mixture and in some patients better control of postprandial glycosuria. But these differences are negligible compared with the smoothness and consistency of control obtained with either of them contrasted with protamine zinc insulin or any combination of it with soluble insulin by separate injection.

13. Eli Lilly & Co., Indianapolis.
14. Peck, F. B.: Personal communication to the authors.

THERAPEUTIC APPLICATION OF IMPROVED PROTAMINE ZINC INSULIN

These two insulins containing 2 parts of soluble (regular or crystalline) insulin and 1 part of protamine zinc insulin, varying only slightly in their accelerated action, were used for routine treatment of a group of 60 patients with severe diabetes mellitus for variable periods up to more than a year. The results appear to justify the use of such a modification in severe diabetes, in which the faults of ordinary protamine zinc insulin are most apparent. The advantages are equally applicable, although less essential, in the more easily controlled, milder forms of the disease.

METHOD OF TREATMENT

Patients.—Sixty diabetic patients were selected for therapeutic tests with the modified insulin. Almost all had established diabetes of greater than average severity. Two thirds were less than 40 years of age, about one fourth less than 20; the youngest was 2 years of age and the oldest 73. The average duration of diabetes for the group was 9.1 years.

Previous Adjustment.—More than 40 of the 60 patients previously had used more than 40 units of insulin daily. The average daily dosage for the entire group was 53 units. Fifty-two of the 60 had used protamine zinc insulin in a single morning dose. Thirty-eight of these had used small supplementary doses of soluble insulin in addition, usually in a single morning injection, rarely twice daily.

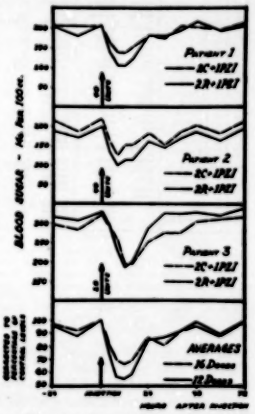

Chart 2.—Comparison of action of 2 to 1 modifications made with regular (amorphous) and crystalline insulin. Both modifications contained only one third of the protamine and zinc present in commercial protamine zinc insulin. The slight difference in action is probably due to inactivation of protamine by foreign protein contained in amorphous insulin. It is not of practical importance. The values obtained in 3 cases are averaged in the lowest curves in terms of percentage of control values without insulin. Peak action at eight to sixteen hours with waning but not exhausted action at twenty-four hours were shown in all cases. These qualities are characteristic of this modification and were the basis for its selection for therapeutic trial.

Their diets provided maintenance calories and protein and intermediate carbohydrate to fat ratios of about 1 to 1 in grams. For the most part they were weighed. Roughly three fourths of the patients were faithful to their diets. Two or 3 were exceedingly careless. Distribution of food into meals was planned according to individual tastes and habits. Most often the meals were approximately equal. A lunch at bedtime usually had been included by patients using larger amounts of protamine zinc insulin.

Previous Control.—Only 3 of the group of 60 had been able to avoid glycosuria with these orthodox methods of management. In half of them glycosuria had been intermittently excessive. Sixty per cent of the group had had frequent or severe

hypoglycemic symptoms on routine management, often while asleep.

In the majority of cases this tendency to intermittent glycosuria or hypoglycemia was striking enough to lead to dissatisfaction with standard methods of control on the part of patient and physician alike. Fully two thirds of the patients using protamine zinc insulin exhibited this inconstant behavior. For the most part, those who failed to do so had mild or early diabetes and were older.

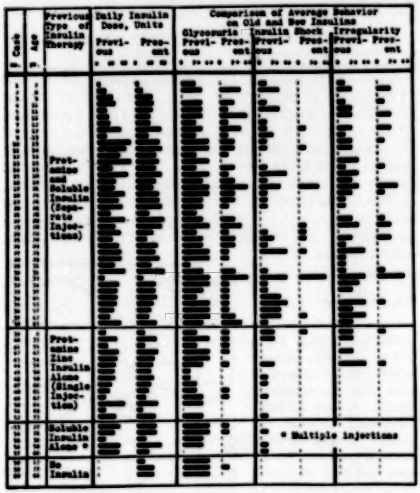

Chart 3.—Results of treatment with a single modification of protamine zinc insulin, usually in one dose daily injected before breakfast. Most of the 60 patients with severe diabetes showed improvement in constancy of control, glycosuria and hypoglycemic shock with the modified insulin (present) as compared with their previous experience with standard insulins, usually in multiple daily injection (previous). There was a slight reduction, on the average, in required insulin.

Chart 3 presents the details of the data just summarized.

Improved Protamine Zinc Insulin.—All patients used the modifications described, which contained 2 parts of crystalline or regular insulin and 1 part of protamine zinc insulin, both in the U-80 strength. All except 3 used only one dose daily before breakfast. Forty-two used a 2 to 1 crystalline mixture (T-1662) mixed in quantity weeks before use and dispensed in ampules.[15] Ten patients used a 2 to 1 regular mixture premixed by u. in ampules from market supplies. Most of the latter could also be satisfactorily adjusted with the crystalline mixture. A few patients mixed insulins in the same proportions in the syringe at the time of injection. No significant differences in results from these various technics were observed. This modification, as shown by chart 2 and the 2 to 1 curve in chart 1, exerts its peak action at eight to sixteen hours after injection, corresponding to the hours of feeding when injected before breakfast. Its effect wanes appreciably after twelve to sixteen hours, corresponding to the hours of sleep. Yet a detectable effect persists into the second day. For these reasons it was selected for routine use.

This modification is stable at ordinary temperatures when premixed. Its p_H is just under 6.0, which is near the isoelectric point for insulin. Its suspension is as easily rendered homogeneous by shaking as protamine zinc insulin. Its crystals are indistinguishable microscopically from those of ordinary protamine zinc insulin. Its supernatant activity is negligible for insulin in solution. After standing, even when buffered to p_H 7.2, there is little increase in supernatant insulin. This is surprising in view of the fact that precipitated insulin redissolves on buffering to this point. This property will be the subject of a subsequent report. It suggests the probability of a compound which does not depend on a component of simple precipitated insulin for its accelerated effect when prepared under the conditions described.

15. Mixed and supplied for us for clinical trial by Eli Lilly & Co.

Adjustment of the diabetes on the modified insulin was accomplished under quantitative conditions in the Evanston Hospital in most cases. Simple substitution of the modified insulin for previous therapy did not as a rule lead to major fluctuation in control. As with commercial protamine zinc insulin, its substitution for soluble insulin previously used alone tended to permit glycosuria for a day or two unless soluble insulin was tapered off.

In all cases the bedtime feeding previously used with protamine zinc insulin was omitted and a midafternoon feeding added. Minor adjustments of the size of the meals frequently were necessary, usually in the form of increased noon or evening meals and reduced breakfasts. Such changes in the detail of the diets, along with adjustments in the size of the dose, usually compensated for individual variations in response to this modification in a single morning dose. More difficulty was anticipated than was experienced from this source. In 3 instances better control was obtained with two doses daily, the smaller at bedtime.

RESULTS

Except for 1 child in whom a respiratory infection developed at the time of transfer, control in all patients was at least as good and usually better with the modification compared with previous standard therapeutic methods. On account of the size of the group, individual quantitative data cannot be presented. It was available for appraisal and was analyzed in the following manner: On the basis of a 4 plus maximum each patient was judged from three standpoints; viz., average amount of glycosuria, frequency and severity of insulin shock and irregularity of control. Appraisal of these indexes of control was intentionally conservative. Chart 3 presents such qualitative data and the dosages used, contrasting the results of the orthodox method with those of the improved methods. The accompanying table summarizes the data.

Comparison of Control Obtained with Usual and Modified Methods of Insulin Dosage in Group of Sixty Diabetic Patients

	Number of Patients Showing Defects of Control			Average Insulin
	Glycosuria	Insulin Shock	Irregularity	Dose, Units
Previous insulin therapy	57	39	36	53
Modified protamine zinc insulin				
Corrected	14	30	30	
Improved	39	4	7	49
Unchanged	7*	0*	9	
Corrected or improved, per cent	88	87	75	50

* One patient worse.

Amount of Glycosuria.—Only 7 of the 57 patients previously showing glycosuria failed to excrete less sugar. Six patients previously unable to keep the urine sugar free without insulin shock were able to do so on a single daily dose of the improved preparation. Twenty-two others showed improvement in glycosuria along with elimination of insulin shock. In the majority the amount of glycosuria was substantially reduced.

Chart 3 reflects this improvement graphically; a summary is given in the table.

Hypoglycemic Symptoms.—Improvement was even more striking in this respect (chart 3 and the table). Thirty patients became free from symptoms of excess insulin after adjustment on the improved modification. In only 9 did such symptoms persist when present previously, and in only 2 of these were they of such consequence as to warrant change of type of management.

Almost no nocturnal insulin shock was observed. That which occurred was mild and was easily recognized and stopped. As might be anticipated, late afternoon symptoms were most common. They were avoided by increases in the size of the lunch or afternoon feeding or both. Evening symptoms were rare, even in the absence of bedtime feedings.

Irregularity of Control.—Improvement in constancy of control was roughly parallel to improvement in glycosuria and hypoglycemic symptoms as described. Of 10 patients previously showing decided irregularities, only 2 continued to do so. These were exceptionally severe "brittle" young patients with diabetes of long standing who were extremely sensitive to insulin and to minor deviations in controlling factors such as exercise and timing of food and insulin. They could not be adjusted satisfactorily on any other combination of protamine zinc insulin and insulin by separate injection. Multiple injections of soluble insulin, including a small dose during the normal sleeping hours, finally produced satisfactory control in them.

Recent experience indicates that this most severe type of diabetes may be controlled even better with one of the intermediate modifications of protamine zinc insulin in two doses daily, a larger dose before breakfast and a smaller one at bedtime. Three similar cases were well controlled on such a program after single doses daily failed to cause consistently good control.

Dosage.—The average dosage required by previous orthodox methods of control was 53 units daily, usually in at least two separate injections. With the modified insulin 49 units daily, on the average, was required by this group. Only 3 patients injected more than one dose daily. It is probable that several others, including the 2 failures, could have been balanced better on two doses daily.

This slight reduction in average required dosage may have been due to fresh quantitative control under hospital conditions. However, it was maintained, as a rule, on return to normal living conditions. It was frequently apparent immediately on transfer from old to new insulins, even though the diet was weighed in both cases. Any common change in feeding conditions was usually in the direction of more generous carbohydrate with the improved insulin, owing to the frequent insertion of an afternoon feeding or increase in the size of the noon and evening meals in fear of insulin shock.

Judged conservatively, it would seem that the 8 per cent improvement in required insulin is significant and due to greater efficiency of the modified protamine zinc insulin. This is even more impressive in view of the fact that multiple injections were avoided as a rule, glycosuria decreased, and a single modification with uniform timing qualities was used in a good sized diversified group of patients with stabilized severe diabetes.

COMMENT

Integration of Time and Intensity Characteristics of Various Protamine Insulins.—Analysis of the timing and intensity properties of the series of variable insulins illustrated in chart 1 demonstrates certain clearcut qualities of each. From the extremes of ordinary insulin at one end of the series to protamine zinc insulin at the other, each preparation shows differences in four major qualities of action, viz., promptness, intensity, duration and uniformity of effect of repeated identical doses. These four qualities bear a constant relationship in each of the different insulins in the series. Other tested intermediate preparations not illustrated fit accurately into the picture.

Soluble insulin acts the most briefly of any in the series. It is also the most prompt and intense in action. Observations not illustrated in this report demonstrate repeated identical doses to be the most uniform in effect,[12] as would be expected in view of its greatest solubility and quickest rate of absorption. These observations are amply confirmed by clinical experience.

As more and more protamine insulin is added to ordinary insulin, the sugar reducing effect is prolonged. Correspondingly, promptness and intensity of action are successively reduced and constancy is sacrificed, as could be expected in view of the fact that solubility and hence absorption rates are decreased.

Protamine zinc insulin as now marketed commercially represents the other extreme, exhibiting the greatest duration of action of the series. Likewise it possesses the qualities of least promptness and intensity and greatest inconstancy of action of repeated doses of the same size, because of greatest insolubility and slowest rate of absorption. Herein lie its chief disadvantages for routine clinical use. Its action is so slow, weak, prolonged and inconstant from dose to dose that glycosuria tends to appear during food absorption and hypoglycemia during fasting, and inconsistent or undulating control tends to follow inconstant absorption of repeated overlapping doses. These characteristics, like those of soluble insulin, are also confirmed by ordinary clinical experience.

The Ideal Combination of Timing and Intensity Qualities.—In the light of these practical pharmacologic properties of such a series of insulins, it is possible to specify which of them should be the ideal preparation for routine daily use. On purely theoretical grounds the ideal insulin is one whose solubility and hence rate of insulin release is such that it acts promptly and intensely enough to control the glycosuria following meals but does not cause hypoglycemia between meals. In order to avoid injections more often than once a day it must act long enough to control overnight hyperglycemia but also wane rapidly enough to avoid nocturnal hypoglycemia. It should possess the greatest possible constancy of action from dose to dose without sacrificing suitable prolongation of effect.

By these standards protamine zinc insulin as now prepared commercially acts unnecessarily long, thereby sacrificing desirable promptness, intensity and uniform absorption capacity. These qualities appear to explain its faults, making it necessary to give supplementary soluble insulin for partial correction of them.

The modification used in the present study corrects those faults automatically by more efficient timing. Its rate of insulin release is such that its strongest effect, when injected before breakfast, covers the feeding period of the day and its waning effect coincides with

fasting during sleep. Yet at twenty-four hours it is still sufficiently active in most cases to avoid the necessity of more than one injection daily. Because of these intermediate properties it is more constant in action on repeated injection than protamine zinc insulin, although not as much as soluble insulin. Thus it retains the advantages of each extreme of the series, largely eliminating the disadvantages of each. It is undoubtedly for these reasons that it permits better control than commercial protamine zinc insulin.

One might object that these considerations may hold true for any given type of diabetes but that sensitivity to insulin varies so widely in different diabetic patients that preconceived properties such as those outlined cannot be fixed arbitrarily. This, in fact, was our expectation when we attempted treatment with a single preparation in a group of patients selected at random. One preparation was used in the hope of realizing simplicity as well as to test the feasibility of treating all patients alike.

We were surprised to discover that the responses were not variable enough to lead to major difficulties in this group of 60 patients representing practically all grades of severity among insulin treated subjects. Better control of almost all patients was established easily with only minor adjustments of the dosage and diet. No variation of the mixture was necessary or even desirable. In only 5 cases of the most severe and "brittle" type adjustment could not be satisfactorily made on a single daily dose of this preparation. They were equally unmanageable on any other combination of protamine zinc insulin and insulin. In 3 of them good balance was obtained with multiple injections of soluble insulin, including 1 during the hours of sleep, proving their inconsistencies due to defects of timing of depot insulins in general rather than to endogenous factors. Three of the 5 difficult cases recently have been satisfactorily balanced on two doses daily of the improved protamine zinc insulin. It seems probable that other similar cases might respond to this variation. If so, another advantage of this modified insulin would be demonstrated.

Extemporaneous Mixtures.—Granting the clinical usefulness of insulins with intermediate timing and intensity qualities, Peck[16] has suggested the expedient of their extemporaneous preparation by mixing in the syringe at the time of injection. In this manner, standard insulins now on the market can be mixed by the patient in the proportions best suited to his particular diabetes. Growing familiarity with the action of mixtures makes this technic fairly common practice among clinicians. Peck has prepared an ingenious table showing the approximate components of ordinary and protamine zinc insulin thought to be contained in such extemporaneous mixtures prepared with various proportions of standard insulins.[16]

There are several valid objections to this technic. First, many patients find it technically difficult to prepare such mixtures in the syringe.[17] They are confused by the use of two insulins with different properties forming another which differs from both. Second, inaccuracies of measurement in a syringe are inevitable. Third, slight variations in excess protamine in protamine zinc insulin of different strengths prepared by different manufacturers would produce major variations in time-intensity effect of comparable mixtures. Finally, a single intermediate preparation apparently satisfies the requirements of the vast majority of diabetic patients and in two daily doses may satisfy all, as just reported. Individualization may be accomplished easily by means of adjustments of the diet and frequency and dosage of a single modification which most nearly satisfies the requirements of the largest number of patients.

16. Peck, F. B.: Action of Insulins, Proc. Am. Diabetes A. **2**: 69-83, 1942.
17. Marble, Alexander: The Treatment of Diabetes with Diet and Insulin, New England J. Med. **224**: 583-586 (April 3) 1941.

SUMMARY

1. Protamine zinc insulin as now prepared commercially possesses inherent faults of timing, owing to slow or uncertain release of insulin from its injection depots. These are seen in diabetic practice as tendencies to glycosuria following meals, to hypoglycemia during fasting, especially at night, and as unpredictable undulations in insulin intensity. For these reasons it is frequently necessary to supplement its action by separate injection of soluble insulin, and even then those tendencies are only partially avoided.

2. The timing and intensity properties of the ideal insulin for routine daily use were analyzed. A modification containing about one third of the protamine and zinc contained in commercial protamine zinc insulin fulfils those requirements most satisfactorily. In actual practice it eliminates the faults of protamine zinc insulin to a large extent. This modification may be prepared from insulins now on the market by mixing 2 parts of soluble insulin with 1 part of protamine zinc insulin, both in the U-80 strength. The time of mixing does not affect the action appreciably. It is stable for months. Slightly more intense action is obtained from mixtures made with regular insulin than with crystalline insulin, probably because of the inert protein content of the former.

3. In most diabetic patients protamine zinc insulin modified in this manner releases insulin from morning depots at a rate which causes moderate increases in intensity when needed during hours of feeding. It also allows decreases when desirable during the hours of sleeping. Therefore better control is obtained with single injections daily than with standard insulins injected more often. Occasional insulin sensitive patients obtain better control with two doses daily, the smaller at bedtime. Successive identical doses are more constant in action than with protamine zinc insulin because of accelerated solubility. Required daily dosage is about 10 per cent less than with ordinary methods because of improved efficiency.

Modification of protamine zinc insulin in this manner results in an insulin which retains all the advantages of protamine zinc insulin and eliminates many of its inadequacies.

636 Church Street.

Principal Drugs of Addiction.—The principal drugs of addiction are opium and its derivatives, morphine and heroin; alcohol, cannabis and cocaine. To this group may be added the barbiturates, paraldehyde, chloral and other depressants, all of which in large dosage over a long period of time may in some persons produce addiction. Of lesser power to cause addiction (or habituation) are such commonly used drugs as nicotine (tobacco), caffeine (coffee, tea, cola drinks), aspirin, acetanilid and bromides. There are, however, a host of compounds and mixtures, many of them proprietary, which are used repeatedly and habitually.—Kraines, Samuel H.: The Therapy of the Neuroses and Psychoses, Philadelphia, Lea & Febiger, 1943.

CHROMOMYCOSIS (CHROMOBLASTOMYCOSIS)

REPORT OF TWO CASES

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AND
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ST. LOUIS

Chromomycosis (chromoblastomycosis), or dermatitis verrucosa, presents a confusing picture at times and consequently a diagnostic problem. The clinical similarity of this disease to syphilis, tuberculosis, neoplasms and other specific and nonspecific granulomas is well known. Although considered to be a disease of the extremities presenting a nodular, verrucoid, papular or granulomatous appearance, reports have shown that the face, neck, chest, shoulders and buttocks also may be affected. Two cases are reported here first because of the varied diagnostic possibilities that they presented and second because of the unusual location of the lesion in 1—the helix of the ear. Phialophora verrucosa was isolated from the first case, which was of several years' duration. Owing to the smallness of the infected area on the ear in the second case and because of a clinical diagnosis of carcinoma, the whole lesion was removed and placed in a fixative. Consequently the organism could not be isolated.

REPORT OF CASES

CASE 1.—*History.*—C. A. C., a white man aged 30, born in Salem, Mo., presented himself in May 1942 at the skin clinic of the Barnard Free Skin and Cancer Hospital complaining of an eruption on the wrist. The patient's family history and past history were irrelevant. His illness had its beginning five years previously as a small "wart," which had gradually increased in size, slightly more rapidly over the past two years. There had been some pruritus for the past six months. No treatment had been attempted, although he had consulted several local physicians. These physicians had referred to the condition as "due to nerves." At the time the lesion developed, he had been working as a farmer. For the past five years he had been working as a pipe fitter.

Examination.—On admission the patient appeared to be well developed and well nourished; he was of small build, weighing 125 pounds (57 Kg.) and measuring 5 feet 5 inches (165 cm.) in height. He was cooperative and intelligent. The ocular and general reflexes were normal. The ears, nose, abdomen, genitalia and extremities were normal. In the right flank he had a well healed scar measuring 8 cm. His teeth were dirty and covered with tartar. There was some pyorrhea with receding of the gums. The tonsils were atrophic. The lungs were clear to percussion and auscultation. The heart tones were equal, regular and without murmurs. The blood pressure was 124 systolic and 86 diastolic.

On the external surface of the left forearm just above the wrist was a circinate, broken plaque 2.5 cm. in diameter, infiltrated and having a depressed atrophic scar in the center (fig. 1). The elevated granulomatous lesion was a reddish pink and had a slightly scaly surface. The diagnoses considered were tuberculosis verrucosa cutis, syphilis, granuloma annulare and porokeratosis.

Laboratory Examination.—Urinalysis was negative. The Kahn reaction was negative. The blood showed 4,890,000 red blood cells, 5,700 white blood cells and 96 per cent hemoglobin. There were 72 polymorphonuclear neutrophils, 26 lymphocytes and 2 mononuclears per hundred white cells.

Studies, observations and reports from the Department of Dermatology, Laboratory for Mycology and Department of Pathology of the Barnard Free Skin and Cancer Hospital, service of M. F. Engman Sr., M.D.

Microscopically, sections of a biopsy specimen showed epithelial hyperplasia, hyperkeratosis and acanthosis with distortion and fusion of the rete pegs. In the upper half of the dermis there was a dense infiltrate made up of lymphocytes, epithelioid cells and many giant cells. In places the epithelioid cells were arranged in nests surrounded by lymphocytes, presenting a picture which was suggestive of tubercle formation. Scattered throughout the infiltrate and within some of the giant cells, however, there were numerous, large, dark brown, thick walled, spherical or irregular organisms. Some occurred singly, others in clumps. These were the characteristic fungi of chromomycosis.

Because of the difficulty in expressing any material from the lesion, a large section of the growth was excised for the purpose of taking a culture. Approximately two thirds of the remaining lesion was removed. This was cut up into small pieces and planted on Czapek's and Sabouraud's dextrose and maltose agars. After four days, small black colonies appeared on and around the implanted tissue. The fungus was identified as Phialophora verrucosa.

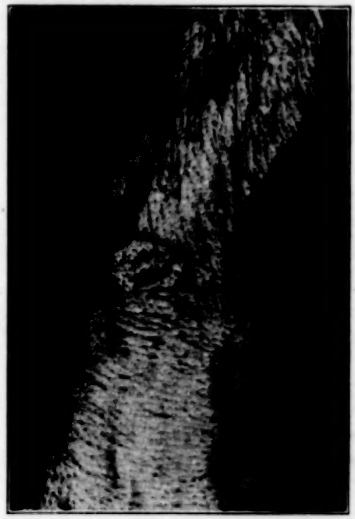

Fig. 1 (case 1).—Verrucous chromomycosis of the wrist of five years' duration.

CASE 2.—*History.*—C. E. D., a white man aged 38, a farmer who had been born and had continuously lived in Missouri, presented himself in May 1942 at the Barnard Free Skin and Cancer Hospital complaining of a "sore" on the right ear. He was assigned to the surgical clinic by the admitting officer. The family history was irrelevant. His past history was essentially negative and did not relate to his complaint on admission. On physical examination his respiratory, cardiovascular and gastrointestinal systems were normal. His present illness had begun two months before, at which time he noticed an eruption on the helix of his right ear. This had slowly increased in size.

Examination.—Just inside the helix of the right ear there was a slightly raised ulcerative area measuring 1.5 by 0.6 cm. There were no palpable nodes in the neck. The clinical diagnosis was squamous cell carcinoma. An excision of the entire lesion and part of the cartilage was recommended. On June 1, 1942 a cautery excision of the lesion, including a segment of the cartilage, was made.

Laboratory Examination.—The surgical specimen consisted of an ellipse of skin measuring 2.5 by 1.5 cm. It showed a nodular, crusted lesion which on section appeared to be woody hard. The process did not involve the underlying cartilage.

Microscopically, a section of the tissue showed epidermal hyperplasia, extensive hyperkeratosis, parakeratosis and acanthosis with a lengthening and distortion of the rete pegs. Extending throughout the upper two thirds of the dermis was an extensive infiltrate made up of lymphocytes, eosinophils, polymorphonuclear leukocytes and numerous giant cells. In the giant cells and also scattered throughout the infiltrate were numerous brown, thick walled organisms. In some of the organisms cross walls could be seen. These were the characteristic organisms of chromomycosis.

HISTORY OF THE DISEASE

The discovery of chromomycosis is attributed to Pedroso, who in 1911 described the first case from Brazil. He called it "black blastomycosis" because of the finding of dark brown cells in the sections of the diseased tissue. In 1920 Pedroso and Gomes [1] published a report of this case with 3 others from Brazil. The organism of each case was named Phialophora verrucosa on the basis of the organism described by Thaxter from the first case reported in the United States in 1915 by Lane [2] and Medlar.[3]

Fig. 2 (case 1).—Section through lesion. Note acanthosis and infiltrate in corium, with giant cell formation. Hematoxylin and eosin stain; reduced from a photomicrograph with a magnification of 145 diameters.

Since 1920, numerous cases of chromomycosis have been reviewed by de Almeida,[4] Moore and Mapother [5] and recently by Weidman and Rosenthal.[6] The last named authors compiled a great deal of the known data on the published cases, listing them as to geographic and anatomic distribution. Of special interest since the review of Weidman and Rosenthal is the publication of Pardo-Castello, Leon and Trespalacios [7] in which 31 cases were reported not only on the extremities but also on the chest, buttock and shoulder.

In spite of the large number of cases reported, including the 2 described here, only 6 have been shown to be due to Phialophora. Of these a Brazilian case was due to Phialophora macrospora and the 5 others were caused by P. verrucosa. In 1915 Lane and also Medlar reported the first case of chromomycosis caused by P. verrucosa, the organism being established taxonomically by Thaxter with a new generic and species determination. The patient was an Italian aged 19 living in the environs of Boston. The organism was isolated from verrucous, nodular lesions on the buttock.

In 1920 Pedroso and Gomes published reports of their 4 cases gathered over a period of several years. Of these 4 cases the 1 described by Pedroso in 1911 showed extensive scarring—the syphiloid type of Pardo-Castello, Leon and Trespalacios—plus verrucous areas; the second showed verrucous, papillomatous lesions with perhaps autoinoculation on the neck; the third showed involvement of the foot with a verrucous patch on the heel, and the fourth showed an extensive involvement of the foot with the lesion extending above the knee to produce the verrucous type with elephantiasis. An organism isolated from one of these cases was shown to be P. macrospora by Moore and de Almeida.[8]

In 1933 Wilson, Hulsey and Weidman [9] described a lesion on the right foot of a 67 year old farmer from Fort Worth, Texas. The lesion had shown a development from a papular to a nodular and verrucous stage with some elephantiasis. The organism isolated from this case was P. verrucosa. In the following year MacKinnon [10] described a case from Montevideo, Uruguay, due to P. verrucosa. The lesion was papular and papillomatous and was located in the region of the anatomic snuffbox of the right hand.

The report of the fourth case in the United States was published by Moore and Mapother. The lesion was crusted, raised and ulcerating, with a pearly border and was located on the right side of the face of a man aged 67. The fungus isolated was P. verrucosa.

The fifth case caused by P. verrucosa and the sixth caused by the genus are described in this paper.

The number of cases occurring in continental United States, with reports published and unpublished, now totals 9. These are listed in the accompanying table.

1. Pedroso, A., and Gomes, J. M.: Sobre quatro casos de dermatite verrucosa producida pela Phialophora verrucosa, Ann. paulist. de med. e cir. **11**: 53, 1920.

2. Lane, C. G.: A Cutaneous Infection Caused by a New Fungus (Phialophora Verrucosa), J. Cutan. Dis. **33**: 840, 1915.

3. Medlar, E. M.: A Cutaneous Infection Caused by a New Fungus, Phialophora Verrucosa, with a Study of the Fungus, J. M. Research **32**: 507, 1915; A New Fungus, Phialophora Verrucosa, Pathogenic to Man, Mycologia **7**: 200, 1915.

4. de Almeida, F. P.: Mycologia Medica; Estudo das mycoses humana e de seus cogumelos, São Paulo, Companhia Melhoramentos, 1939, p. 583.

5. Moore, Morris, and Mapother, Paul: Chromomycosis of the Face: Report of a Case and a Study of the Causative Organism, Phialophora Verrucosa, Arch. Dermat. & Syph. **41**: 42 (Jan.) 1940.

6. Weidman, F. D., and Rosenthal, L. H.: Chromoblastomycosis: A New and Important Blastomycosis in North America: Report of a Case in Philadelphia, Arch. Dermat. & Syph. **43**: 62 (Jan.) 1941.

7. Pardo-Castello, V.; Leon, E. Rio, and Trespalacios, F.: Chromoblastomycosis in Cuba, Arch. Dermat. & Syph. **45**: 19 (Jan.) 1942.

8. Moore, Morris, and de Almeida, F. P.: Etiologic Agents of Chromomycosis (Chromoblastomycosis of Terra, Torres, da Fonseca and Area Leão, 1922) of North and South America, Rev. biol. e hyg. **6**: 94 (Dec.) 1935; New Organisms of Chromomycosis, Ann. Missouri Botan. Garden **23**: 543, 1936.

9. Wilson, S. J.; Hulsey, Sim, and Weidman, F. D.: Chromoblastomycosis in Texas, Arch. Dermat. & Syph. **27**: 107 (Jan.) 1933.

10. MacKinnon, J. E.: Estudios del primer caso uruguayo de cromoblastomicosis y "revista critica" sobre la enfermedad, Arch. urug. de med., cir. y especialid. **5**: 201 (Aug.) 1934.

DESCRIPTION OF ORGANISM

Owing to the fact that a clinical diagnosis of squamous cell carcinoma was made in the second case and the lesion completely excised and placed in a fixative, it was impossible to obtain any cultures. Cultures from the first case, however, were obtained by seeding tubes of medium with finely cut up tissue obtained by biopsy.

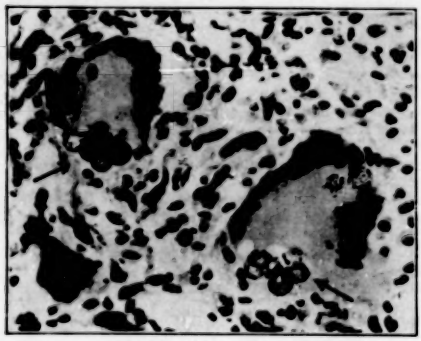

Fig. 3 (case 1).—Brown, thick walled cells of Phialophora verrucosa in giant cells. Hematoxylin and eosin stain; reduced from a photomicrograph with a magnification of 710 diameters.

The organism when seen in tissue consists of spherical or irregular sclerotic cells which are thick walled, dark brown or chestnut colored and simple or multiple, appearing in clusters. The cells reproduce by enlargement and septum formation to produce the mulberry-like groups. Budding of these fungi is not a characteristic form of reproduction in tissue. These cells may be seen distributed throughout the affected tissue, in microabscesses surrounded by polymorphonuclear

Fig. 4 (case 2).—Section through ear lesion. Note thickening of tissue due to hyperplasia with acanthosis. Hematoxylin and eosin stain; reduced from a photomicrograph withh a magnification of 10 diameters.

leukocytes or engulfed by giant cells. In old lesions or necrotic tissue the cells may occasionally germinate to produce short filaments.

Tissue implants on Czapek's and Sabouraud's dextrose and maltose mediums resulted in small black colonies which appeared after four days on and around the inoculums. When the colonies developed to a suitable size, subcultures were made on various mediums. The organism microscopically was identified as Phialophora verrucosa.

The growth of P. verrucosa on artificial mediums both macroscopically and microscopically has been well described. The strain isolated here is essentially similar microscopically to the strains isolated from Boston, Fort Worth, Montevideo and St. Louis.

In culture, the thick walled brown cells germinate to form multiseptate hyphae. These vary in form and size from 2 to 5 microns in diameter, depending on the medium on which the fungus is growing. As the organism grows, it forms various morphologic structures which are modified by the ingredients of the medium. The hyphae are seen as multiseptate filaments occurring singly or in bunches (coremioid), simple or somewhat branched. The cells are either elongated or short. The latter may be seen also in chains, as spherical cells, moniliform in appearance. This type of cell formation is characteristically found growing in all mediums but

Fig. 5 (case 2).—Section through ear lesion showing profuse cellular infiltrate with organisms, giant cells and many leukocytes. Hematoxylin and eosin stain; reduced from a photomicrograph with a magnification of 145 diameters.

is a prominent feature on sugar mediums. Chlamydospores may also be seen. These either occur terminally or may be found intercalary. They are thick walled, large and spherical and simulate those seen in the infected tissue. On certain mediums, such as Loeffler's agar, these cells assume a close similarity to the sclerotic forms seen in sections of diseased tissue.

The reproductive organs of P. verrucosa, the phialides—cuplike structures with endogenous spore formation—develop in most mediums but are most prevalent on synthetic mediums such as Czapek's agar (fig. 7). These spore bearing structures develop terminally, laterally or alternately on a hypha, are single or many celled, simple or branched, short or long. The spores or conidia arise endogenously and are expelled from the cuplike portion of the phialide. They collect at the

mouth of the phialide in a group and are held together by a mucilaginous material termed gloea. The phialospores or conidia are at first small, spherical to ovoid cells and then become elongated or fusiform to measure approximately 1 to 3 by 2 to 4 microns. These spores germinate to reproduce the structures noted.

Grossly, after fifteen days, growth on Czapek's agar P. verrucosa attained a colony size of 3.5 cm. in diameter (1, fig. 8). A central button was formed with the mycelium both aerial and subsurface. The color varied from an olivaceous brown to blue-black. On corn meal agar, after the same period of growth, the colony reached a diameter of 3.2 cm. (2, fig. 8). A central button with sector formation was produced. The color was dark gray to black. On the peptone agar growth was comparatively slow, with a diameter of 1.5 cm. after fifteen days (3, fig. 8). The colony was compact and showed aerial mycelium which was a dark gray, but the compact portion of the growth was black. On Sabouraud's medium, both dextrose and maltose, the growth was essentially similar. The colony on the dextrose medium reached a diameter of 2.8 cm. (5, fig. 8), while on the maltose agar it was 2.5 cm. (4, fig. 8). The cultures were sharply defined with some aerial growth. The color was slate gray to black. The growth on potato-dextrose agar measured 3 cm. in diameter after fifteen days (6, fig. 8). The colony showed a central knob with evidence of slight concentric growth. The color varied from light to dark olivaceous gray.

CLINICAL FEATURES

Chromomycosis clinically is seldom recognized except perhaps in areas in which the disease flourishes and presents characteristic verrucous lesions on the extremities. With the exception of these typical cases, the disease has perhaps never been diagnosed clinically. The first indication of the correct determination has come from the pathologist, who found the sclerotic, dark brown, thick walled cells in the tissue section. Like blastomycosis, coccidioidal granuloma, syphilis and neoplasms, this relatively recently recognized disease, chromomycosis, presents a number of gross clinical features which may be confusing and misleading.

Chromomycosis has generally been considered to be a disease of the extremities. Recent reports, including the 2 cases presented in this paper, indicate that lesions may occur on almost all parts of the human skin. These include, in addition to the hands and feet, the wrist, arm, shoulder, neck, face, ear, chest, abdominal region, thigh, knee and leg. However, the greater number of cases show the lesions on the extremities. The reason for this is that the primary lesion in many instances has apparently been the result of a traumatic infection with contaminated material. The larger number of patients were farmers, workers of the soil or its products. This has certainly been true of the 3 patients observed in St. Louis.

Clinically, chromomycosis presents lesions which may be papular, verrucous or papillomatous, nodular, ulcerative, psoriasiform, granulomatous, with or without abscess formation and with rarely any suppuration except when due to secondary infection with bacteria. Scaliness is often a feature. Pain or pruritus rarely occurs. Visceral or skin metastases have been reported only in 2 cases, 1 from Algeria [11] and one from Puerto Rico.[12] Systemic invasion is not a feature of chromomycosis. Bone involvement likewise has not been reported. Lymphangitis and adenopathy (regional) may occur but are usually attributed to secondary infection. As the disease progresses and persists, there is cicatrization such as is found in blastomycosis. On the extremities the progressive formation of additional lesions accompanied by tissue reaction may result in elephantiasis. The enlargement of the foot in these cases resembles Madura foot.

Chromomycosis in Continental United States

Geographic Location	Color and Sex	Age	Occupation	Anatomic Location	Type of Lesion	Duration, Years	Organism	Year Seen	Authors
Boston	White man	19	?	Buttock	Nodular verrucous, necrotic	1	Phialophora verrucosa	1915	Lane,[2] Medlar [3]
Fort Worth, Texas	White man	67	Farmer	Right foot	Warty, papular and nodular, verrucous, elephantiasic	40	Phialophora verrucosa	1931	Wilson, Hulsey and Weidman [9]
Durham, N. C.	Negro	47	Farmer	Left hand, arm	Nodular verrucous, elephantiasic	4	Hormodendrum (Fonsecaea) pedrosoi	1935	Martin, Baker, Conant (Am. J. Trop Med. 16:503, 1936)
St. Louis	White man	67	Log hauler	Right side of face	Crusted, ulcerative, pearly border	10	Phialophora verrucosa	1938	Moore and Mapother [5]
Miami, Fla.	Negro	43	Cook, but injury from oar	Left hand, dorsum	Warty, nodular, verrucous	30	?	1939	Sams—unreported
Atlanta, Ga.	White men	68	Farmer	Left wrist, dorsum	Raised, boggy mass, points of discharge	3 mos.	Fonsecaea pedrosoi	1939	Emmons, Halley and Halley (J. A. M. A. 116:25, 1941)
Philadelphia	Negress	44	?	Left ankle	Verrucous, granulomatous, with abscesses	7 or 8	Fonsecaea pedrosoi	1940	Weidman and Rosenthal [8]
St. Louis	White man	30	Farmer	Left wrist	Granulomatous, verrucous	5	Phialophora verrucosa	1942	Moore, Cooper and Weiss
St. Louis	White man	38	Farmer	Helix right ear	Raised, ulcerative	2 mos.	.....	1942	Moore, Cooper and Weiss

The basis of the reports in the literature and on their series of 31 cases, Pardo-Castello and his associates classified chromomycosis into five clinical types: 1. The verrucous or papillomatous type, which begins as a group of small nodules or papules with a scaly surface. These nodules increase in size and usually form large circular masses which tend to heal in the center with scar formation. Abscesses may be found in the area of granulation tissue, but suppuration does not result. The appearance is not unlike that of blastomycosis or tuberculosis verrucosa cutis. Case 1 is a good example of this most common type. 2. The tuberculoid type, which is in all probability an early

11. Montpellier, J., and Catanei, A.: Mycose humaine due à un champignon du genre "Hormodendrum: H. algeriensis, nov. sp.," Ann. de dermat. et syph. 8:627 (Nov.) 1927.

12. Carrión, A. L., and Koppisch, E.: Observations on Dermatomycosis in Puerto Rico: Report of a Case of Chromoblastomycosis, Puerto Rico J. Pub. Health & Trop. Med. 9:169 (Dec.) 1933.

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form of verrucous chromomycosis, also resembles tuberculosis verrucosa cutis or sarcoid. The lesions begin as small patches or nodules with erythematous areolas and little scaling. 3. The syphiloid form, which is nodular and scaly, with some erythema. The nodules are small, flattened and serpiginous, annular or arcuate

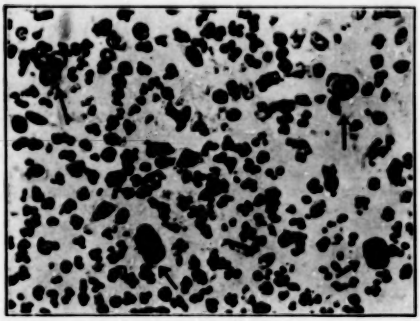

Fig. 6 (case 2).—Section through ear lesion showing brown, thick walled cells of the organism and many polymorphonuclear leukocytes. Hematoxylin and eosin stain; reduced from a photomicrograph with a magnification of 910 diameters.

in their arrangement. The lesions may resemble a superficial late syphiloderm. Ulceration with a hypertrophic base may be present due to granulation tissue. The surface may be covered with crusts. 4. The psoriasiform type, which consists of superficial inflammation and infiltration with the lesion covered with thick white adherent scales. Abscesses and verrucous patches are not observed and the lesion resembles psoriasis. 5. The fifth group, which is made up of those lesions which become cicatrized and those which result in the elephantiasic enlargement of the extremities. This group no doubt represents an end result or an advanced stage of chromomycosis, since scarring is found in lesions of long duration and swelling of the affected areas does occur when there is a multiplicity of lesions. The usual features of verrucosities, abscesses, ulceration and scaling may be present. The resemblance to Madura foot has been noted previously.

It would seem therefore that, because of the varied appearance of the lesion, chromomycosis should be differentiated clinically from various mycotic granulomas, including coccidioidal granuloma, blastomycosis and maduromycosis or Madura foot, from tuberculosis verrucosa cutis, syphilis, epithelioma, psoriasis, leishmaniasis [13] and, as discussed by Carini,[14] from sarcoid, pyoderma vegetans, yaws, porokeratosis, granuloma annulare, mossy foot and no doubt other clinical entities.

MICROSCOPIC OBSERVATIONS

A clinical diagnosis has seldom been made except in the case of typical lesions. The task of determining the cause of the infection has invariably fallen to the microscopist. The diagnosis is readily made by finding the characteristic fungous cells in the diseased tissue.

Microscopically, the lesions of chromomycosis show a number of features which are compatible with the general picture seen in sections of blastomycosis, tuberculosis and other mycotic granulomas. There are, however, certain characteristics which may serve to differentiate the disease.

The epidermis shows hyperkeratosis and acanthosis with a thickening, broadening and elongation of the rete pegs. Within these pegs may be seen microscopic abscesses filled with polymorphonuclear leukocytes, cellular débris and the fungous cells. At times within these areas one may also find Langhans giant cells containing fungi.

The most pronounced changes are found in the dermis. Here one sees edema, a pronounced cellular infiltration and, in older lesions, evidence of fibrosis. The cellular infiltration is made up of polymorphonuclear leukocytes, lymphocytes, epithelioid cells, plasma cells, eosinophils and Russell's fuchsin bodies, which have been noted in tissue sections by others. Giant cells of the foreign body or Langhans type may be present as well as macrophages. There is sometimes a tendency to pseudotubercle formation in the infiltrate. Fibroblastic changes may occur. Necrosis and microabscesses such as are found in Gilchrist's disease are not prominent in chromomycosis. The sclerotic cells of the fungus are found scattered throughout the corium, especially in the abscesses or in giant cells. They occur either as single cells or in mulberry-like clusters.

A comparison of our 2 cases of chromomycosis is of interest. The first case, of five years' duration, presented a clinical picture which could easily have been mistaken for tuberculosis verrucosa cutis or syphilis (fig. 1). Microscopically the picture presents the characteristics seen in typical chromomycosis (fig. 2). Characteristically tubercle-like formation is seen. Distributed through these cellular masses, both free and in giant cells, are the fungous cells of P. verrucosa (fig. 3).

In the second case, apparently of two months' duration, the physical examination revealed a slightly ulcer-

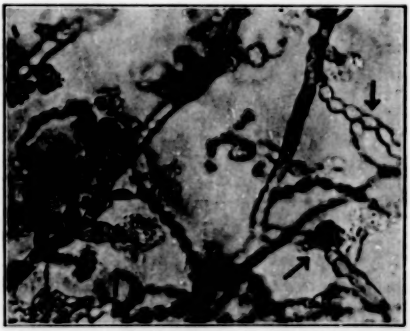

Fig. 7.—Six days growth of Phialophora verrucosa on Czapek's agar (subculture). Note phialides, groups of spores and moniloid formation. Reduced from a photomicrograph with a magnification of 1,160 diameters.

ated lesion somewhat infiltrated. The clinical diagnosis of squamous cell carcinoma indicates clearly the diagnostic difficulties. Microscopically, the section of tissue shows thickening and edema with hyperplasia, hyperkeratosis and acanthosis (fig. 4). This lesion, representing an early infection, shows also the extensive infiltration with the various types of cells so noticeable

13. Terra, F.; Torres, M.; da Fonseca, O., and Arêa Leão, A. E.: Novo typo de dermatite verrucosa mycose por Acrotheca com associação de leishmaniose, Brasil med. 2: 363 (Dec. 9) 1922.

14. Carini, A.: Sur la dermatite verruqueuse, Bull. Soc. path. exot. 17: 227 (March) 1924.

in chromomycosis. Here, however, the granulomatous changes are not particularly prominent. Instead, there is seen a general infiltration of many types of cells, including some giant cells (fig. 5). Fibrosis, so apparent in older, chronic lesions, is absent. Edema with consequent swelling is evident. Dispersed throughout this rich cellular infiltrate, of which the greater number of cells are polymorphonuclear leukocytes, are seen the sclerotic cells of the fungus (fig. 6).

PROGNOSIS AND TREATMENT

Chromomycosis is not a fatal disease. It is a disease of slow evolution, as has been pointed out. The prognosis is good unless there is a secondary complication of tuberculosis, leishmaniasis, as in the case of Terra, Torres, da Fonseca and Aréa Leão, or some other fatal disease. Scar formation may result in loss of use of the affected limb, if the scarring is severe enough to cause retraction of the tissue. In the elephantiasic type of lesion there may result loss of use of the limb, either temporary or permanent, because of the excess weight and because of stiffening of the joints.

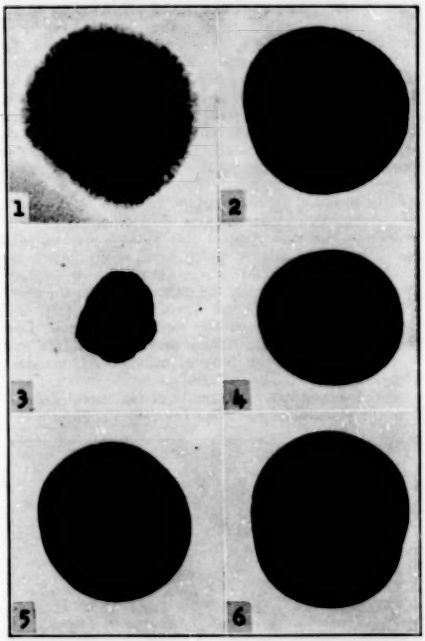

Fig. 8.—Phialophora verrucosa. Actual size after fifteen days' growth: 1. Czapek's agar. 2. Corn meal agar. 3. Peptone agar. 4. Sabouraud's maltose agar. 5. Sabouraud's dextrose agar. 6. Potato-dextrose agar.

Therapy for chromomycosis has not been encouraging in most cases. Iodides by mouth or intravenously have not met with success in all cases. Usually this form of therapy has been supplemented with roentgen irradiation. In such instances it is difficult to evaluate the therapeutic agents individually. Moore and Mapother's patient showed good results with a rapid clearing of the lesion following the use of iodides by mouth. On the other hand, Pardo-Castello and his co-workers found no improvement in the majority of their cases after the administration of iodides by mouth or intravenously. Roentgen irradiation may be of great value in localized patches of chromomycosis. In the unpublished case of Sams, potassium iodide was given by mouth, 30 grains (2 Gm.) three times a day, and filtered roentgen rays subintensively, 225 roentgens for four months at monthly intervals. The lesion responded very well, leaving a thin scar.

Pardo-Castello and his associates used intensive ray therapy, 600 to 1,200 roentgens filtered through 1 or 2 mm. of aluminum, depending on the thickness of the lesion, with benefit. If the lesions are not too extensive, cauterization, electrocoagulation or surgical excision may be successfully employed. In 1 of our 2 cases surgical excision and complete removal of the lesion brought about an apparent cure.

The use of thymol internally, 1 Gm. daily before breakfast, has been of no value. The various organic salts of antimony and copper, colloidal copper intravenously and the sulfonamide group of drugs were of no benefit in the cases in which these were tried by Pardo-Castello.

When the lesion is small, therefore, the treatment may be either iodides and roentgen radiation, electrocoagulation or surgical excision. When the lesion is extensive, it is a matter of experimentation. If the lesion results in elephantiasis of the extremity, perhaps the only recourse lies in amputation.

COMMENT

Chromomycosis is rapidly assuming a place of importance in dermatology. The discovery of many cases in the past few years does not necessarily mean that the incidence of the disease has become higher. Certainly in cases in which biopsy was not done routinely the clinical diagnoses of tuberculosis verrucosa cutis, blastomycosis or the various other previously mentioned entities could have been made. It may be that closer attention is now being paid to the microscopic and clinical features of chromomycosis by clinicians who have become better acquainted with the disease.

There are several additional features of chromomycosis which have not been mentioned but should receive just a few words in passing. In the first place, the disease is practically universal in its geographic distribution. Reports of chromomycosis have come from North, Central and South America, the West Indies, Europe, Asia and Africa. It is not entirely a disease of the tropics, as was first thought. Two cases from Canada have recently come to the attention of one of us (Moore).

Chromomycosis occurs chiefly among farmers or those associated with farm produce. There have been some exceptions, but a careful search into the history of the particular patient has invariably disclosed some association with vegetation. The 2 cases presented here were no exceptions.

Age is not a causative factor in this disease. The patients have varied considerably in their ages. De Almeida listed 54 cases, of which 43 occurred between the ages of 10 and 80; the ages in the other 11 cases were not classified. Pardo-Castello and his associates found that the ages in their 31 cases varied from 14 to 70. Most of the lesions have occurred in the age

range of 30 to 50 years. The disease is found chiefly among males, with only 4 reported among females.[15] The worldwide distribution of the disease indicates that all races and nationalities may be susceptible.

Chromomycosis has a slow evolution. Many of the cases reported by Pardo-Castello and his co-workers had a duration of twenty to twenty-five years. Wilson, Hulsey and Weidman's case had a duration of forty years.

It is agreed by all observers of the disease that it is not truly a blastomycosis. This has been emphasized in published articles stressing the fact that the fungus either in tissue or in culture does not bud but divides by cross wall or septum formation. The term chromoblastomycosis, as originally described by Terra, Torres, da Fonseca and Aréa Leão, was therefore revised by Moore and de Almeida [8] to chromomycosis. This name, besides being shorter, eliminates the possibility of confusing the disease with blastomycosis. The objection raised to retaining the term chromomycosis is that it may be confused with chromophytosis (pityriasis or tinea versicolor). However, "chromophytosis" is rarely used and should not, therefore, cause any concern to dermatologists, since they prefer the term pityriasis (tinea) versicolor. It is obvious that unless the term chromoblastomycosis is abandoned the confusion of this disease with blastomycosis must be expected.

SUMMARY AND CONCLUSIONS

The 2 cases of chromomycosis presented are the eighth and ninth cases respectively occurring in continental United States. One was of five years' duration and was caused by Phialophora verrucosa. This represents the sixth case due to the genus Phialophora and the fifth caused by P. verrucosa.

The lesion in the first case occurred on the left wrist, was verrucous and granulomatous and was difficult to differentiate clinically from tuberculosis verrucosa cutis, syphilis, granuloma annulare, porokeratosis and blastomycosis. The microscopic features of chromomycosis in general and of this lesion in particular were examined. An analysis of the histopathologic features indicates that the infection had all the characteristics of a granulomatous lesion of chromomycosis, with tubercle-like formation. The organisms were profuse in the infected tissue.

The infection in the second case was primary on the helix of the right ear and was of two months' duration. The lesion was raised and ulcerative and clinically was diagnosed squamous cell carcinoma. A cautery excision of the lesion was done. Since the excised tissue was placed in a fixative, the causative agent could not be cultured. Microscopically, the section of tissue showed features characteristic of chromomycosis. However, instead of the granulomatous tissue changes so noticeable in the sections of the first case, an infiltration of various types of cells, chiefly polymorphonuclear leukocytes, was present. Dispersed throughout this infiltrate were many fungous cells.

The organism is similar microscopically to other strains isolated at Boston, Fort Worth, Montevideo and St. Louis.

Washington and Theresa avenues.

15. Tschernjawski, J.: Chromoblastomycosis, Arch. f. Dermat. u. Syph. **157**: 196, 1929. Kano, Kwaüchiro: Ueber die Chromoblastomykose durch einen noch nicht als pathogene beschriebenen Pilz: Hormiscium dermatitidis, n. sp., ibid. **170**: 282, 1937. Mérine, Jacques: A propos de la clinique de la chromomycose: Cas de chromomycose de la peau avec lésion des ganglions lymphatiques régionaux, Ann. de dermat. et syph. **9**: 122 (Feb.) 1938. Weidman and Rosenthal.[9]

METABOLIC STUDIES IN PATIENTS WITH CANCER OF THE GASTRO-INTESTINAL TRACT

V. PANCREATIC INSUFFICIENCY IN A PATIENT TREATED SURGICALLY FOR CARCINOMA OF THE AMPULLA OF VATER

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The exclusion of the pancreatic juice from the intestine resultant to resection of the duodenum or of the head of the pancreas frequently is followed by a disorder marked by an increase in the quantity of nitrogen, fat and starch eliminated in the feces.[1] Whereas it would be supposed that the disorder could be controlled by the administration of pancreatic secretions, the results of the small numbers of reported studies of the procedure are not uniform.[2]

A patient has been studied who had undergone a resection of the duodenum for carcinoma of the ampulla of Vater and who presented the clinical picture of pancreatic deficiency. The results of this study suggest an effective therapeutic procedure, which may be useful in the management of other cases of this type.

TABLE 1.—*The Excretion of Nitrogen in the Stools and the Urine and the Excretion of Fat in the Stools of the Patient Under Study*

	Daily Diet			Feces			
Days	Fat, Gm.	Protein Nitrogen, Gm.	Calories	Fat, Gm. per Day	Fat, per Cent of That Ingested	Nitrogen, Gm. per Day	Nitrogen, per Cent of That Ingested	Urinary Nitrogen, Gm. per Day
9	36	10.1	2,400	32.7	95	4.9	48	5.2
8	45	10.0	2,400	39.5	87.5	3.9	39	3.2

MATERIAL

The patient was a woman aged 39 who originally was admitted to the hospital with jaundice, acholic stools, bile in the urine and an abdominal mass. The first stage of the operation consisted of a cholecystogastrostomy. In the second stage a gastroenterostomy was made, the head of the pancreas was resected, the pancreatic ducts and the common bile duct (distal to the cystic duct) were ligated and excised, and finally the pylorus with the duodenum and ampulla of Vater was resected. During the one year interval before she was readmitted to the hospital her stools always were voluminous, soft and gray but not acholic. There was a loss of weight of 15 pounds (6.8 Kg.).

From the Memorial Hospital for the Treatment of Cancer and Allied Diseases.
Dr. Rekers is a trainee in the diagnosis and treatment of cancer, National Cancer Institute, National Institute of Health, United States Public Health Service.
The authors received assistance from the Jane Coffin Childs Memorial Fund for Medical Research, the Standard Brands, Inc., and the National Cancer Institute.

1. Beazell, J. M.; Schmidt, R. C., and Ivy, A. C.: The Diagnosis and Treatment of Achylia Pancreatica, J. A. M. A. **110**: 2735-2739 (June 21) 1941. Coffey, R. J.; Mann, F. C., and Bollman, J. L.: The Influence of the Pancreas on the Utilization of Foodstuffs, Am. J. Digest. Dis. **7**: 144-149 (April) 1940.
2. Whipple, A. O., and Bauman, L.: Observations on the Pathologic Physiology of the Insular and External Secretory Functions of the Human Pancreas, Am. J. M. Sc. **202**: 629-636 (May) 1941.

Six hospitalized subjects were studied as controls. They were admitted for the treatment of disorders entirely unrelated to the gastrointestinal tract.

METHODS

The diets fed to all the subjects during the period of study contained constant, known amounts of fat, protein and carbohydrate, taken in three equal meals daily. A single source of meat was used. The protein and fat contents of the diets of the patient and of two of the controls (L. D. and A. F.) were established by analysis.[3] The intakes of the other persons studied were calculated from tabulated values (tables 1 and 2). During the period of observation no gastrointestinal disorders were noted in the control subjects. The control subjects and the patient were kept on the constant intake for five days before the collection of stools and urine was begun. In the course of the study certain dietary supplements were added.

The methods used for the collection of stools and of urine and for the determination of stool lipid have been described in a previous publication of this series.[3a] The stool lipid content was calculated in terms of the "stearin equivalent" and is expressed throughout this communication as "stool fat." The nitrogen in the stools and the urine was determined by means of a micro-Kjeldahl technic.[3b]

RESULTS

The control subjects were observed over periods which varied in length from four to seventy days. None excreted in the stool a daily average of more than 5.6 Gm. of fat or 1.5 Gm. of nitrogen (table 2).

The findings in the patient were strikingly abnormal.[4] During two separate control periods of eight and nine days (table 1) the average daily amounts of fat excreted in the feces were 39.5 and 32.7 Gm., and the average amounts of nitrogen 3.9 and 4.9 Gm. daily. Thus, from 87.5 to 95 per cent of the fat and from 39 to 48 per cent of the nitrogen ingested was lost in the feces.

The excess of nitrogen excreted in the feces of the patient under study readily was demonstrated to be of dietary origin. When the diet was altered to contain only 0.2 Gm. of protein nitrogen for a period of nine days the output of nitrogen in the feces rapidly decreased to an average daily value of 2.2 Gm. The addition of 6 Gm. of amino acid nitrogen [5] per day during another period of seven days did not increase significantly the fecal output. This observation indicated that the digestion of protein was impaired and not the absorption of the simple end products of protein breakdown (table 3). It was not feasible to study in a similar fashion the effects of decreasing the fat content of the diet.

In view of the considerable surgical reconstruction of the patient's gastrointestinal tract, two possible causes

TABLE 2.—*The Excretion of Nitrogen in the Stools and the Urine and the Excretion of Fat in the Stools of the Control Subjects*

Subject	Disorder	Days	Daily Diet: Fat, Gm.	Daily Diet: Protein Nitrogen, Gm.	Daily Diet: Calories	Feces: Fat, Gm. per Day	Feces: Fat, per Cent of That Ingested	Feces: Nitrogen, Gm. per Day	Feces: Nitrogen, per Cent of That Ingested	Urinary Nitrogen, Gm. per Day
L. D.	Oral leukoplakia	4	35	10.1	2,400	4.2	12	1.0	10	9.0
A. F.	Hemangioma of foot	7	35	11.2	2,400	3.3	9.5	0.85	8	10.35
P. P.	Plantar wart	4	135	16.0	2,580	5.6	4	1.5	9	14.6
P. R.	Varicose veins	7	105	14.4	2,130	3.9	4	0.7	5	13.8
A. S.	Osteitis fibrosa cystica	48	75	18.0	1,800	2.1	3			
I. D. V.	Xeroderma pigmentosa	70	60	12.0	1,228	3.0	5			

TABLE 3.—*The Decrease in Fecal Nitrogen Following a Low Protein Intake; the Effect of the Addition of Amino Nitrogen Supplements on the Excretion of Nitrogen by the Patient Under Study*

Days	Daily Diet: Fat, Gm.	Daily Diet: Protein Nitrogen, Gm.	Daily Diet: Calories	Supplement	Feces: Fat, Gm. per Day	Feces: Fat, per Cent of That Ingested	Feces: Nitrogen, Gm. per Day	Feces: Nitrogen, per Cent of That Ingested	Urinary Nitrogen, Gm. per Day
9	80	0.2	2,000	.....	48	56.5	2.2	..	3.1
9*	36	10.1	2,400	.....	32.7	95	4.9	48	5.2
9*	45	10.0	2,400	.....	39.5	87.5	3.9	39	3.2
7	34	9.5	2,470	6 Gm. amino acid nitrogen.....	35.3	104	4.1	49	5.7

* Basal.

TABLE 4.—*The Effect of the Addition of Bile Salts, of Lipocaic and of Pancreatic Digestive Enzymes to the Diet on the Excretion of Fat and Nitrogen by the Patient Under Study*

Days	Daily Diet: Fat, Gm.	Daily Diet: Protein Nitrogen, Gm.	Daily Diet: Calories	Supplement	Feces: Fat, Gm. per Day	Feces: Fat, per Cent of That Ingested	Feces: Nitrogen, Gm. per Day	Feces: Nitrogen, per Cent of That Ingested	Urinary Nitrogen, Gm. per Day
4	26	10.3	2,400	Bile salts, 1.8 Gm.....	41.9	117	7.0	68	4.5
6	34.5	9.85	2,200	Lipocaic, 6 Gm.....	36.1	105	4.35	45	2.9
2	45	10.0	2,400	Pancreas extract, 25 Gm.....	24.2	54	2.4	24	8.0
2	43	9.0	2,200	Pancreas extract, 25 Gm.....	17.2	40	1.9	20	8.8
2	45	10.1	2,400	Pancreas extract, 25 Gm.....	13.7	32	0.3	3	7.5

3. (a) Rekers, P. E.; Abels, J. C., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: IV. Fat Metabolism; A Method of Study, J. Clin. Investigation, to be published. (b) Robinson, H. W.; Price, J. W., and Hodgen, C. G.: The Estimation of Albumin and Globulin in Serum, J. Biol. Chem. **120**: 481-498 (Sept.) 1937.

4. For the purpose of clarity, the experimental periods of this patient are not presented in chronological order.

5. Amino acids, Frederick Stearns & Co., Detroit.

existed for the functional disorder: the exclusion of extrinsic pancreatic secretion and the altered flow of bile into the intestine. Accordingly, 1.8 Gm. of bile salts [6] was administered daily for four days, but this induced only diarrhea and greater excretion of both fat and nitrogen (table 4).

TABLE 5.—*The Effects of the Addition of Dietary Protein and Fat Supplements on the Excretion of Fat and Nitrogen by the Patient Under Study*

	Daily Diet			Feces			
Days	Fat, Gm.	Protein Nitrogen, Gm.	Calories	Fat, Gm. per Day	Fat, per Cent of That Ingested	Nitrogen, Gm. per Day	Nitrogen, per Cent of That Ingested	Urinary Nitrogen, Gm. per Day
5*	36	10.1	2,400	32.7	91	4.9	48	5.2
6*	45	10.0	2,400	39.5	87.5	3.9	39	3.9
7	98	23.0	3,000	31.1	33.5	6.5	28	3.5
9	89	0.2	2,000	48.0	58.5	2.2	..	2.1

* Basal.

Pancreatic enzymes were next tested. The daily ingestion of 6 Gm. of lipocaic,[7] a material obtained from pancreas which has to do with certain phases of the internal metabolism of fat, was without significant effect. As a source of enzymes of the external secretions of the pancreas, 25 Gm. of Pancreatin [8] then was administered each day for six days. The daily excretion of fat in the stool fell rapidly and progressively from an average basal level of 36.1 Gm. to only 13.7 Gm., or from 91 to 32 per cent of the amount ingested. Likewise the daily fecal output of nitrogen decreased progressively from an average basal level of 4.4 to 0.3 Gm., or from 44.5 per cent to 3 per cent of that ingested as protein (table 4). Associated with this striking change, the frequency, the bulk and the foul odor of the stools were reduced.

The daily dose of pancreas extract was decreased to 12 Gm. per day for the next twenty days, and definite clinical improvement occurred. It was not feasible during that period to make further determinations.

During the course of this study it was possible to ascertain certain relationships between the fat and nitrogen contents of the diet and the amounts of those substances excreted. The administration of a supplement of 53 Gm. of fat and 13 Gm. of protein nitrogen (table 5) with the constant diet resulted in a relative decrease in the excretion of both these substances. The daily absorption of the total amount of fat increased from about 4 to 62 Gm. and of nitrogen from about 5.6 to 16.5 Gm. When nitrogen intake was decreased the total amount of fat excreted increased, which suggested that at least part of the effect noted in the preceding period might have been due to the high protein content of the diet.

COMMENT

Pronounced loss of fat and nitrogen was observed in a patient whose pancreatic ducts had been ligated during resection of the head of the pancreas and duodenum. The possible causes for the excess excretion were considered to be (*a*) an inability to digest fat and nitrogen into those compounds which could be absorbed, (*b*) an inability to absorb even simple fat and nitrogen compounds or (*c*) an excess intestinal secretion of fat and nitrogen compounds.

Oral administration of protein split products (amino acids) did not increase the nitrogen content of the feces, and a lower protein intake was followed by a definite reduction. Hence it appears that the abnormal output of stool nitrogen, at least, is due to the inability of the patient to digest protein.

Of the therapeutic materials which seemed likely to be useful for this patient, external pancreatic enzymes were by far the best, whereas lipocaic and bile salts were without effect. A regimen based on a diet composed of the easily absorbed foodstuffs, namely amino acids, fatty acids and simple monosaccharides, is not practicable. The use of a diet high in its content of fat and protein apparently did increase the patient's ability to absorb these foodstuffs, but it increased the bulk of the stools and the discomfort of the patient.

SUMMARY

A patient who had had the duodenum and the head of the pancreas resected and the pancreatic ducts ligated presented the clinical picture of pancreatic insufficiency. The administration of large quantities of pancreatic enzymes was followed by conspicuous clinical benefit and by a significant decrease in the amounts of fat and nitrogen excreted in the feces. An increase in the protein content of the diet resulted in increased absorption of fat. An increase of the fat content of the diet resulted in an increase of fat absorbed but no lessening of fat lost.

6. Bilein, Abbott Laboratories, Chicago.
7. Lipocaic, Eli Lilly and Company, prepared according to the method of Dragstedt.
8. Pancreatin, Parke, Davis & Company, enteric coated.

Clinical Notes, Suggestions and New Instruments

MENINGOMYELITIS
A COMPLICATION OF PRIMARY ATYPICAL PNEUMONIA

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Numerous reports have appeared in the literature of the last two years pertaining to an acute pulmonary infection characterized by cough, general malaise and hyperpyrexia associated with a relative leukopenia. The mortality rate is low and the physical findings are described as minimal. Roentgenograms uniformly reveal patchy, veil-like shadows involving areas of the lung much greater in area than would be suspected from the physical examination. Various names have been applied to this syndrome, such as "pneumonitis" and "virus pneumonia." More recently the descriptive title "pneumonia, primary, atypical, etiology unknown" has been adopted as official nomenclature by the Medical Departments of both the Army and the Navy.

A survey of the current literature indicates that complications of this increasingly prevalent pulmonary infection are few, the disease tending to run a self-limited course without sequelae. This observation is further confirmed by a review of 150 cases admitted to the Medical Division of the hospital at which we are stationed. It is our purpose in this report to describe the occurrence of an unusual and serious involvement of the central nervous system apparently developing as a direct sequel to primary atypical pneumonia.

The patient, a naval officer aged 37, was in good health until Sept. 20, 1942, when he began to complain of headache, chills and general malaise. The following day the temperature rose to 101 F. and he developed a paroxysmal, hacking cough productive of a moderate amount of mucopurulent sputum and frequently followed by regurgitation of food. He was ordered to bed by his physician and was treated symptomatically. He

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responded well enough to be placed on light duty about one week after the onset of his illness. The second day out of bed, however, his symptoms recurred and once again he developed chills, fever and extreme weakness.

On the tenth day after onset he entered the hospital, ambulatory, and did not appear to be seriously ill. His temperature was 102 F., the pulse rate 95 per minute and respiratory rate 18 per minute. Physical examination revealed that the pharynx was injected, the nose obstructed and an inspiratory lag was present on the left side of the chest with slight impairment and decrease in breath sounds at the left base. It was noted that the reflexes were equal and active and that no Babinski reflex was present. The leukocytes numbered 11,700 with 72 per cent neutrophils, the sedimentation rate was very rapid (29 in 30 minutes), the sputum showed a few diplococci and the blood culture was sterile. X-ray examination of the chest revealed mottled and homogeneous densities in both lower lung fields, consistent with a primary, atypical pneumonia.

The patient was treated symptomatically with salicylates, gargles and ephedrine nasal spray.

The second evening in the hospital the patient's temperature rose to 104 F. and he became extremely prostrated and vomited repeatedly. It was noted that the cough was incessant but the coughing effort weak and nonproductive. The bladder was found to be much distended although the patient experienced no discomfort whatever from this source. One thousand cc. of urine was obtained on catheterization. There was also a temporary loss of control of the rectal sphincter.

A neurologic examination revealed that the patient was slightly irrational, his voice feeble and his cough reflex considerably diminished. His respirations were entirely abdominal with no apparent movement of the intercostal muscles. The cranial nerves were intact and the sensory system unimpaired. There was extreme motor weakness of both extremities. The knee and ankle reflexes were hyperactive on both sides. Reflexes in the upper extremities were equal and active. There were bilateral Babinski and Chaddock signs, and the abdominal and cremasteric reflexes were absent. A lumbar puncture was done at this time and a slightly cloudy fluid under pressure of 250 mm. was obtained. The cell count was 221 with 87 per cent lymphocytes; total protein was 40 mg.; sugar was 90.9 mg. and the Kahn reaction and colloidal gold test were negative. Bacteriologic study of the fluid was negative. The patient apparently had a meningomyelitis of the lower lumbar region with patchy involvement of the spinal cord at higher levels. The findings indicated that the pathologic changes were limited to the motor system of the anterior and lateral columns of the cord; hence the absence of sensory findings. The etiologic agent was possibly blood borne via the anterior and ventral spinal arteries and their corona vasorum. The type of involvement is comparable to that noted in poliomyelitis except for the presence of hyperactive deep tendon reflexes (a sign pathognomonic of involvement of the pyramidal or corticospinal pathway in the lateral columns). The pronounced distention of the urinary bladder without subjective symptoms of discomfort and without evidence of obstruction of the lower urogenital tract could be explained only on the basis of bladder atony secondary to cord involvement.

Respiration became increasingly difficult and, in the absence of a mechanical respirator, the special watch was increased to provide personnel for continuous artificial respiration. The urinary retention was overcome by the installation of a retention catheter, and the bladder was irrigated twice daily.

In addition, repeated injections of hypertonic dextrose (25 per cent solution) were given and oxygen was administered continuously by means of the B. L. B. mask.

During the next twenty-four hour period there was definite improvement in respiration and a noticeable decrease in the signs and symptoms of general toxemia.

On the fifth hospital day the patient appeared to be greatly improved. His temperature was 100 F., respirations were normal and slight movement of his legs was noticed. Massage and passive motion were instituted to maintain tonicity and circulation of the muscles. He continued to improve gradually, and one week after admission a spinal fluid examination showed that the cell count had decreased from 221 to 41, protein from 40 to 25 mg. and sugar from 90.9 mg. to 64.5 mg.

Specimens of spinal fluid and blood were submitted to the Department of Infectious Diseases of the National Institute of Health. The report indicated that no recognizable virus was demonstrated by animal inoculation, although special search was made for the various neurotropic viruses, influenza A and B and Q fever.

On the eighth hospital day the retention catheter was removed and the patient gradually regained the ability to void spontaneously. At this time the paralysis of his legs began to disappear rapidly and he soon regained voluntary control of the muscles.

The deep and superficial reflexes of the trunk and lower extremities returned to normal coincidentally with the disappearance of the motor paralysis.

Except for a mild cystitis, his recovery proceeded uneventfully and he was discharged from the hospital one month after admission. After return to duty slight weakness in the legs and paresthesia of the toes were noted for a short time.

COMMENT

Myelitis is a not uncommon complication of severe infections such as syphilis, tuberculosis, typhus, diphtheria, typhoid and smallpox. The deleterious effects on the cord may be produced by direct action of the bacteria or by their toxins. During World War I and in the decade following this period a number of reports are to be found in the literature[1] which describe the occurrence of myelitis secondary to respiratory infections of various types.

In these cases the onset of the disease was marked by an upper respiratory infection, pain in the chest and severe generalized muscular pains. Later paresis developed in one or more of the extremities with pronounced reduction or abolition of the deep tendon reflexes. There were a concomitant disturbance of sphincter control and objective sensory disturbances both deep and superficial. The spinal fluids were uniformly reported as normal. The majority of these patients recovered in thirty to sixty days without any residual symptoms. As the study of these cases did not include roentgenograms of the chest it is possible that some, at least, were examples of primary atypical pneumonia.

A review of the literature has failed to reveal a report of myelitis occurring as a complication in a proved case of primary atypical pneumonia.

The complete recovery of the patients described in the 1917-1925 reports paralleled the situation in our own case and was in decided contrast to the types of myelitis produced by known bacterial infections, which usually result in prolonged illness and often leave the patient with permanent motor and sensory disabilities.

The case here described differs from those previously reported in the following features: (*a*) It occurred in a proved primary, atypical pneumonia; (*b*) there was no sensory involvement which could be objectively demonstrated; (*c*) the spinal fluid was distinctly abnormal. The symptomatology, spinal fluid findings and clinical course of the disease were closely comparable to those of other conditions known to be produced by virus invasion of the central nervous system. If this assumption is correct, it tends in a limited way to support current views with regard to the etiology of primary atypical pneumonia.

SUMMARY

1. A severe but transient meningomyelitis occurred as a complication of primary atypical pneumonia.

2. The character of the primary disease was established by physical and roentgen examinations and by the clinical course.

3. The principal neurologic manifestations were interference with the muscles of respiration, bladder atony, loss of sphincter control and paralysis of the lower extremities, all developing on the twelfth day of the disease.

4. The patient subsequently recovered without evidence of residual neurologic disability.

1. Holmes, Gordon: Acute Febrile Polyneuritis, Brit. M. J. 2: 37 (July 14) 1917. Bradford and others: Acute Infective Polyneuritis, Quart. J. Med. 12: 89 (Oct.) 1918. Strauss, Israel, and Rabiner, A. M.: Myeloradiculitis, Arch. Neurol. & Psychiat. 23: 240 (Feb.) 1930. Sands, I. J.: Acute Benign Infectious Myelitis, J. A. M. A. 96: 23 (Jan. 3) 1931. Greenfield, J. G.: Acute Disseminated Encephalomyelitis, a sequel to "Influenza," J. Path. & Bact. 33: 453 (April) 1930.

Council on Industrial Health

THE COUNCIL ON INDUSTRIAL HEALTH HAS PREPARED THE FOLLOWING REPORT AS AN AID TO PHYSICIANS IN INDUSTRY AND TO COMMITTEES ON INDUSTRIAL HEALTH IN STATE AND COUNTY MEDICAL SOCIETIES CALLED ON TO FORMULATE STANDING ORDERS FOR INDUSTRIAL NURSES.

C. M. PETERSON, M.D., Secretary.

STANDING ORDERS FOR NURSES IN INDUSTRY

For some time the medical and nursing professions have been concerned about the employment of nurses in industry without adequate medical supervision. The Council on Industrial Health has therefore been requested to formulate standing orders for industrial nurses which can be adapted to meet the requirements of individual industrial medical departments. If no responsible industrial medical authority exists, it is recommended that the nurse request helpful instruction in this regard from the committee on industrial health of the appropriate county or state medical society.

GENERAL RELATIONSHIPS

Standing orders represent a preliminary understanding between physician and assisting personnel about routine conduct of a medical service. In establishing such orders in an industrial medical department, several considerations need to be borne in mind:

1. The greater the amount of personal supervision exercised by the physician directly in the industrial environment, the better is the industrial health service.
2. Standing orders cannot be written to meet every situation likely to arise in industry. They must be modified to meet specific requirements and in accordance with the training and professional competence of the assisting personnel. They should be signed by the supervising medical authority and posted prominently in the medical department.
3. The nurse in industry should assume no responsibility for service outside the field of her professional training. This applies particularly to individual case management, from which the nurse should rigidly abstain except:
   (*a*) In emergencies demanding immediate independent judgment and action.
   (*b*) Procedures of preliminary or first aid nature routinely required by reason of the nature of the work and which are clearly stipulated in the standing orders.

This statement confines itself mainly to these last named aspects of mediconursing relations in industry. Additional reports on other functions of industrial nurses will follow as needed.

EMERGENCY PROCEDURE IN INDUSTRY

General principles which operate in all emergency situations apply to industry as well. They are:

1. Call a physician immediately.
2. Stop bleeding.
3. Restore breathing.
4. Prevent shock and infection.
5. Do no more than is actually needed.

The supervising physician should assure himself that these instructions are thoroughly understood and should institute special training when necessary. Nurses in industry should qualify as first aid instructors.

Emergency Supplies.—Emergency packs with essential sterile supplies should be available at all times in the medical department and in first aid kits suitably located throughout the plant. Regular inspection is necessary.

Hemorrhage.—Bleeding calls for immediate attention. The nurse should notify the physician and, until he arrives, proceed as follows:

1. Expose the wound.
2. Remove obvious foreign matter.
3. Apply pressure.

Direct manual or bandage pressure firmly applied over sterile gauze packing at the bleeding site will effectively control moderate hemorrhage. Indirect compression is indicated in excessive bleeding not controllable by direct methods. Digital compression over the vessel against underlying structures either adjacent to the wound or at the nearest pressure point will usually suffice until the physician arrives. Indirect pressure should be applied proximal or distal to the wound, in keeping with the arterial or venous character of the bleeding. Hemostats or clamps should be applied whenever the emergency warrants it.

Avoid applying a tourniquet if possible. If severe bleeding in an extremity suggests the use of a tourniquet, apply a blood pressure cuff.

The nurse should remember that:

1. A direct pressure bandage should not act as a tourniquet.
2. A tourniquet must be periodically released at least every fifteen minutes.
3. No dressing should be applied over a tourniquet.
4. Asepsis must be observed at all times.

Asphyxia.—Cessation of breathing from any cause demands:

1. Artificial respiration *at once* and *at the site of the accident.*
2. Notification of the physician.
3. Maintenance of body warmth. Avoid excessive heating.

All industrial nurses should demonstrate ability to apply artificial respiration by the prone pressure method and should realize the need for its continuous application until breathing is restored or until careful repeated medical examination advises otherwise.

Shock.—Early and adequate shock treatment is life saving. Do not delay.

Common symptoms of shock following injury are pallor, perspiration and rapid thready pulse. Emergency management by the nurse should include:

1. Notification of the physician.
2. Removal of cause. If shock is due to hemorrhage, control it. If it is due to trauma not associated with bleeding, all active treatment of injury should be deferred until shock management has been instituted. Wounds should be covered with sterile dressings to prevent infection.
3. Relief of pain: ⅛ to ¼ grain (0.010 to 0.016 Gm.) of morphine sulfate, repeated if necessary, or barbiturates as routinely ordered except in injuries to the head or trunk.
4. Keeping the patient warm, dry, and on his back with his head low. Avoid overheating.

ROUTINE NURSING CARE OF INJURIES

Successful medical management of industrial injuries depends on:

1. Prompt treatment.
2. Meticulous cleansing and dressing.
3. Examination of deep as well as of superficial structures.

To accomplish these aims the routine functions of the nurse should be confined to care of minor wounds as follows:

1. Protect wound with sterile gauze while adjacent area is cleansed with soap and water or solvent.
2. Discard protective dressing and clean wound margins.
3. Irrigate wound with sterile water or isotonic solution of sodium chloride.
4. Apply antiseptic of physician's choice.
5. Apply dry sterile dressing, interfering as little as possible with function. Sterile dressings should be covered with protective material for use at work. The worker should be instructed not to remove the dressing but to return to the medical department if it becomes loosened or uncomfortable.

The nurse should do no more than is actually needed. The following conditions require direct medical supervision:

1. Wounds requiring débridement.
2. Those with obvious or suspected involvement of deep structures.
3. Wounds with edges which do not approximate.
4. Wounds about the head and face.
5. Contaminated wounds requiring tetanus prophylaxis.

Management of Common Injuries.—Injuries most likely to be encountered in industry include the following conditions:

1. Abrasions: Clean and apply dry dressing. Extensive or deep loss of skin, especially about the fingers and hands, needs medical attention.
2. Contusions: Treat with cold compresses directly following injury, later with moist heat. If soreness or disability persists or if deep involvement is suspected, refer to the physician.
3. Lacerations: Clean and apply dressing as directed. Any possibility of injury to joints, nerves or tendons should be brought to the physician's attention at once.
4. Puncture Wounds: Puncture wounds through the skin need direct medical supervision to avoid or treat severe infection. If superficial, clean and apply sterile dressing.
5. Slivers and Splinters: Penetration through the skin by slivers or splinters always carries the risk of an infected puncture wound and should be treated as such. Those lodged superficially and easily removed without added trauma or incision may be extracted aseptically by the nurse.
6. Burns and Scalds: Clean minor burns with soap and water. Apply petrolatum or 5 per cent boric acid ointment, bandaging firmly without interfering with function. Leave blisters alone.

   In all other cases:

   (*a*) Notify the physician.

   (*b*) Cover the burned area with a sterile dressing or sheet moistened with isotonic solution of sodium chloride or 5 per cent sodium bicarbonate solution.

   (*c*) Combat pain and shock.

In the absence of specific orders, chemical burns should be treated by irrigation or immersion in water for at least twenty minutes and then by dressing.

7. Sprains and Strains: Treat first with cold compresses, elevation of the part and rest. A physician's advice is necessary regarding strapping, other methods of support or fixation, further examination or special therapy.

FRACTURES

Preliminary steps for the nurse are:

1. Call a physician at once.
2. Keep the patient quiet and warm.
3. Immobilize before any movement is attempted.
4. Do not attempt reduction.
5. If the fracture is compounded, cover the site of the fracture with a dry sterile dressing. *Do not cleanse or reduce.*

Special instruction in splinting should be provided every industrial nurse.

EYE INJURIES

Rigid aseptic technic must be scrupulously observed in all eye conditions. Never attend consecutive patients without sterilization of instruments and careful hand washing. Remember that early symptoms of infection simulate foreign body.

Minor Burns.—Do not apply ointments to minor burns of the skin about the eye. Apply a sterile dressing and refer to the physician.

Burns of the Eye.—1. Chemical Burns: Irrigate chemical burns of the eye *copiously* and *at once* with water, preferably by immersion. Neutralizing solutions are usually inadequate or unavailable. The rapidity with which the irrigation occurs is more important than the type of solution used. Continue to irrigate at least twenty minutes by the clock.

2. Hot Metal Burns: Apply a sterile pad and refer at once to the physician. Do not irrigate. An anesthetic should be applied as ordered by the doctor.

Every burn of the eye should receive competent medical attention early.

Foreign Bodies.—The nurse should attempt to remove only those foreign bodies of the eye which can be readily located and which can be easily washed out or removed with a dry sterile cotton applicator. An antiseptic may be applied if the physician so orders.

Direct medical care is essential:

1. If the foreign body cannot readily be located. Stains to aid in the location of foreign bodies should be used only on specific medical order.
2. If removal requires any instrumentation.
3. If irritation or pain persists after removal.

No person with an eye injury should be discharged without examination by a physician.

"Flash" Injury.—First aid treatment should include:

1. Local anesthetic as ordered.
2. Cold compresses.
3. Sedatives.

Persistent pain following flash needs medical examination and treatment.

Conjunctivitis.—Conjunctivitis or other forms of conjunctival irritation should be referred routinely to the physician or ophthalmologist.

HEAD INJURIES

Until the physician takes over, the nurse should:

1. Keep the patient lying down.
2. Elevate the head.
3. Apply ice cap or cold compress. *No sedatives.*
4. Record pulse and respiration every ten minutes.

Clip or shave and cleanse areas adjacent to scalp lacerations, and cover with a sterile pad.

CHEST AND ABDOMINAL INJURIES

Contusions of the chest and abdomen with or without external evidence of injury may result in trauma to underlying organs. Until seen by the physician, such patients must be:

1. Kept warm and quiet.
2. Allowed no sedatives.
3. Have pulse, temperature and respiration recorded frequently.
4. Suitably bandaged to avoid contamination.

In case of abdominal injury give nothing by mouth.

NONOCCUPATIONAL ILLNESS

Treatment of injury or illness which has no relation to occupation is not a function of the industrial medical department except:

1. First aid for emergency sickness. Such measures as the situation demands must be taken until notification of the family physician discharges responsibility.
2. For minor ailments which temporarily interfere with an employee's comfort or ability to complete a shift and for the relief of which a physician would not ordinarily be consulted.

In all relationships of this kind, judgment and tact are required of the industrial nurse. Several principles apply:

1. Before giving any treatment, the temperature, pulse, general appearance and a history of the presenting complaint should be recorded.
2. Palliative treatment, especially for chronic or recurring disorders, should not be repeated.

Every properly trained nurse understands the difference between attention of this kind and systematic treatment.

CARE OF MINOR ILLNESS AND SYMPTOMS

Persistent or augmenting symptoms of irritation, discomfort or disability suggest faulty work environment. The nurse should not hesitate to ask for medical examination of workers and of the premises.

Fever.—A rise in temperature of 1 degree suggests medical consultation before work is resumed. Findings should be checked by repeated thermometer recordings.

Headache.—Record temperature. If headache is accompanied by dizziness, nausea, vomiting, stiff neck, injury, history of recurrence, fever, general malaise or other symptoms the patient

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needs medical attention. If not, give an analgesic as ordered by the physician.

Remember that headache or dizziness may be premonitory signs of intoxication.

Unconsciousness.—1. Fainting. Usual symptoms are pallor, with shallow breathing, slow and weak pulse. Period of unconsciousness is of short duration.

Keep the patient lying down with head lowered until fully recovered. Be sure the patient has plenty of fresh air. Clothing should be loosened and stimulating inhalants used, such as ammonia or smelling salts.

2. Other causes. If other signs are present or if unconsciousness persists longer than a few minutes, call for medical assistance. *Give nothing by mouth.*

Toothache.—If there is a cavity, the nurse may pack it with cotton dipped in oil of cloves for temporary relief. For further examination and treatment refer to a dentist.

Nosebleed.—Spontaneous nosebleed may be treated by cold packs or pinching the sides of the nose against the septum. Keep the patient sitting erect or standing and loosen the collar if it tends to constrict the neck. Advise the patient not to breathe or blow through the nose for an hour or two after bleeding has stopped.

Bear in mind that certain occupational exposures are manifested by nasal damage and bleeding.

Sore Throat.—Patients with sore throat may be given a hot saline gargle if they have a normal temperature. Do not "paint" the throat. Any persistent sore throat or one associated with fever needs medical care at home.

Respiratory Irritation or Infection.—Repeated or persistent signs of bronchial or chest irritation without associated infection suggests an unfavorable occupational exposure. A plant hygiene survey is indicated.

Persons having acute respiratory infections with elevated temperature, cough, sneezing or nasal discharge should be sent home for proper segregation, rest and medical attention. In mild infections, work may be continued if under medical or nursing supervision simple measures will control symptoms and prevent spread.

Available medical evidence at the present time cannot support routine administration of cold vaccines or vitamin preparations as methods of reducing the incidence or severity of acute respiratory infections.

Frequent colds or chronic respiratory conditions require special medical consideration.

Abdominal Distress.—Early signs of occupational intoxication may be abdominal in character. In any case abdominal distress, nausea or pain, especially if severe or persistent, requires competent medical diagnosis and management.

Laxatives should never be dispensed from an industrial medical department.

Dysmenorrhea.—Painful menstruation not associated with fever or gastrointestinal disturbances may be treated with an analgesic ordered by the physician and the patient placed at rest with heat to the lower part of the abdomen. If there is no relief or if other signs or symptoms present themselves, she should be referred to her physician.

Patients with recurrent severe dysmenorrhea should not be given palliative treatment. They should be referred for examination and treatment.

DERMATITIS

Management of skin disorders in industry depends on cause.

Specific Irritants.—Materials or processes in the plant capable of causing skin disease should be identified and special orders provided for control. Competent dermatologic consultation is essential in all obscure or refractory situations.

Nonspecific Skin Disease.—Nonspecific skin irritation in industry is almost entirely assignable to faulty personal hygiene. The nurse can do much to improve washing routine, the use of dependable protective coverings, the wearing of clean work clothing, maintenance of satisfactory housekeeping in the plant and the general maintenance of accepted hygienic procedure.

PREGNANCY

A definite policy regarding employment during pregnancy should embrace the following recommendations:

1. The employee should notify the proper authority in industry about her pregnancy within the first trimester.
2. She should obtain a statement from her own physician—
   (*a*) That her work is not contraindicated.
   (*b*) Regarding the length of time she should work.
3. Special attention should be given to the nature of the work. Pulling, pushing and lifting must be kept within safe limits. Rest periods will tend to minimize emotional and physical instability during pregnancy.
4. Ordinarily work should terminate by the thirty-second week (within six weeks of term). If contraindications arise within this period, the employment should stop.
5. Return to work is inadvisable before six weeks after delivery and then only on notification of the employer by the physician.

EQUIPMENT AND SUPPLIES

Space which can command privacy and which can be kept clean and properly prepared for emergency and routine services by the nurse should be provided in the plant. Special attention should be given to heating, light, ventilation and accessibility.

Furnishings and Supplies

General Furnishings:

1. Sink
2. Instrument cabinet
3. Sterilizer
4. Dressing table
5. Leg rest
6. Cot
7. Stretcher
8. Mirror 10 by 12 inches
9. Foot-pedal waste can
10. Waste basket
11. Storage cabinets
12. Paper towel rack
13. Adhesive rack
14. Record file
15. Scale

Instruments and Supplies:

1. Scalpels
2. Splinter forceps
3. Tissue forceps
4. Hemostatic forceps
5. Bandage scissors
6. Surgical scissors
7. Hand magnifying glass
8. Syringes
9. Assorted hypodermic needles
10. Assorted surgeons' needles
11. Needle holder
12. Assorted bandages
13. Adhesive plaster
14. Cotton
15. Applicators
16. Assorted sutures
17. Assorted splints
18. Assorted jars and basins
19. Test tubes
20. Safety razor and blades
21. Hot water bottle
22. Ice cap
23. Crutches
24. Tourniquet

Drugs: (as ordered by the physician or medical adviser)

1. A stimulant
2. An emetic
3. Analgesics and sedatives
4. Antiseptics

The accompanying check list of furnishings and supplies suitable for a small plant dispensary should be augmented by equipment for emergency treatment or other special medical requirements as ordered by the plant physician or other medical adviser.

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(*a*) The Industrial Medical Department.
(*b*) Plant Hygiene Studies.
(*c*) Outline of Procedure for Physicians in Industry.
(*d*) Women in Industry.
(*e*) Control of Common Respiratory Infections.
(*f*) Indiscriminate Administration of Vitamins to Workers in Industry.
(*g*) Recognition and Prevention of Industrial Dermatitis.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

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SATURDAY, AUGUST 28, 1943

INSECT VECTORS OF POLIOMYELITIS

In 1911 Flexner and Clark [1] allowed flies to feed on the spinal cords of monkeys which had died of experimental poliomyelitis. Insects thus contaminated harbored infectious doses of the virus for at least forty-eight hours. This observation was followed by a long series of experiments by other investigators [2] in which unsuccessful attempts were made to transmit poliomyelitis to rhesus monkeys by houseflies, biting flies, body lice, head lice, bedbugs, fleas and mosquitoes. In face of these repeated failures, supplemented by the growing belief that poliomyelitis is a "respiratory disease," entering the body only through the olfactory nerves, many clinicians believed that it was "unnecessary" to try to bring insects into the epidemiologic picture.

Twenty years later, however, following a shift of clinical interest to the possibility that human feces and sewage might be the main sources of infection, insect vectors again became of logical interest. Rosenow [3] reported that flies collected during the 1935 Kentucky epidemic harbored infectious doses of poliomyelitis virus, typical paralysis developing in 1 out of his 3 rhesus monkeys inoculated intracerebrally with fly filtrates. These results were challenged by other investigators,[4] who reported only negative results with houseflies, mosquitoes and other insects collected during other epidemics.

Methods of detecting poliomyelitis virus in stools and sewage have been greatly improved since that time, the most important improvement being the substitution of highly susceptible Java monkeys (cynomolgus) for the more resistant rhesus and green African monkeys previously used. Adopting these newer methods, three groups of investigators [4] reported positive results with fieldflies collected in epidemic areas. A detailed account of the results obtained by one of these groups is currently reported by the late Dr. James D. Trask and his colleagues [5] of the Department of Pediatrics of Yale University.

During the 1941 epidemic of poliomyelitis the Yale investigators caught numerous samples of nonbiting fieldflies in traps set within the yard near the privy or near a house in which 1 or more cases of poliomyelitis had occurred. Samples of biting insects were also collected from the backs or sides of cows tethered in the epidemic areas. The flies were usually transferred to glass jars and stored at refrigeration temperature for a period of three to seven days before using. Two types of inoculums were prepared from these insects. In the first type 100 to 600 dead flies together with the inside contaminated surface of the glass container were washed with 50 cc. of distilled water. The washings were centrifuged at low speed and the midlayer set aside for nasal instillations. Fifteen per cent ether was added to the remaining parts of the washings for bactericidal purposes. The etherized sample was used for intra-abdominal injections. In their second type of inoculums from 100 to 500 flies were emulsified in 200 cc. of distilled water. The resulting emulsions were centrifuged and prepared in the same way for inoculation tests.

Thirty-nine washings or emulsions representing 19 different fly samples were each inoculated into 1 monkey. In most cases the inoculation was made by two routes: 2 cc. given intranasally on each of three successive days, and 10 to 20 cc. of the etherized preparation given intra-abdominally as one dose. Animals subsequently showing signs of poliomyelitis were killed and studied microscopically, and attempts were made to pass the virus to a second generation by means of multiple intracerebral inoculations. Briefly summarized, poliomyelitis virus was definitely isolated and identified from 4 of the 19 different fly samples, with "equivocal" results from a fifth sample. Positive results were obtained with doses representing as few as 14 flies (average 70 flies). All positive results were obtained with cynomolgus monkeys, all tests with rhesus and green African monkeys being negative. No positive takes were obtained with the mosquitoes and biting flies similarly tested.

The nonbiting fly species showing positive results did not differ from those giving negative reactions. The dominant species in each group were green bottleflies and blowflies, the common housefly being present in small numbers in only 2 of the 4 positive specimens.

1. Flexner, Simon, and Clark, P. F.: Contamination of the Fly with Poliomyelitis Virus, J. A. M. A. **56**: 1717 (June 10) 1911.

2. Kling, C.; Pettersson, A., and Wernstedt, W.: Com. Inst. méd. Etat. Stockholm **3**: 5, 1912. Anderson, J. F., and Frost, W. H.: Pub. Health Rep. **28**: 833 (May 2) 1913. Clark, P. F.; Fraser, F. R., and Amoss, A. L.: J. Exper. Med. **19**: 223, 1914. Sawyer, W. A., and Herms, W. B.: Attempts to Transmit Poliomyelitis by Means of the Stable Fly (Stomoxys Calcitrans), J. A. M. A. **61**: 461 (Aug. 16) 1913. Noguchi, Hideyo, and Kudo, R.: J. Exper. Med. **26**: 49 (July) 1917.

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5. Trask, J. D.; Paul, J. R., and Melnick, J. L.: J. Exper. Med. **77**: 531, 545 (June) 1943. Dr. Trask died on May 24, 1942.

Practically the same results had been previously reported by Sabin and Ward,[6] who were able to isolate poliomyelitis virus from 8 of 15 samples of fieldflies collected during 1941 outbreaks of the disease. Their positive results also were obtained with cynomolgus monkeys. Their fly pools also usually consisted mainly of green bottleflies and black blowflies. Toomey, however, reported one successful take with a rhesus monkey inoculated intracerebrally with an emulsion of fieldflies trapped near an open sewer during the same epidemic.

Trask's positive results were all from fly samples collected near a potential (though not proved) source of virus in the form of "exposed" human feces of recent origin. The Yale investigators, however, warn against reading an epidemiologic implication into their results, since the presence of virus in their positive samples might be merely a "resultant" and not a "causal factor" in the local epidemic. Whether or not the virus can multiply on or within the contaminated flies has not yet been determined.

OBSTETRIC AND PEDIATRIC CARE OF WIVES AND INFANTS OF ENLISTED MEN

California and Western Medicine for August 1943 takes to task the action of the federal Children's Bureau in providing payment for the obstetric care of the wives of enlisted men and for the care of their children; objection is not made to the payment or to the care but to the technic and rate of payment. Incidentally, the editorial in *California and Western Medicine* asks why the "national mouthpiece of organized medicine" has made no editorial comment and calls attention to what are said to be the only two items on the subject which appeared in THE JOURNAL. Elsewhere in this issue (Organization Section, page 1257) appears some of the correspondence on the subject between Dr. George H. Kress, Secretary-Editor of the California Medical Association, and Dr. Olin West, Secretary of the American Medical Association.[1]

The readers of *California and Western Medicine* should have the accurate information here published.

The article by Dr. Edwin F. Daily in THE JOURNAL for July 31, 1943 indicates that the program which received its first special appropriation in March 1943 was already operating by July 31 in thirty-seven states, Hawaii, Alaska and the District of Columbia and that the health agencies of several of the remaining eleven states were at the time completing their plans for administering the program. More than 95 per cent of payments were for maternity care and less than 5 per cent for pediatric care. It will be observed that under this program plans are developed and administered by state health agencies and then approved by the chief of the Children's Bureau.[2]

At the meeting of the House of Delegates held this year in Chicago several resolutions were introduced relating to this activity of the Children's Bureau. The House of Delegates was confronted with a proposal from the state of New York to the effect that the federal security law be changed in such manner as to assure payment of the physician and with another resolution presented by Dr. John H. Fitzgibbon of Oregon to the effect that approval be expressed of federal assistance to the wives and children of servicemen provided that any funds allocated for professional services be given to the wives of enlisted men, such patients then to secure the services of physicians as they themselves deemed proper and the fees for professional services to be decided by mutual agreement between the patients and the attending physicians. The reference committee of the House of Delegates brought in a report that the action of the federal government in making funds available for maternity and infant care for the wives of enlisted men be approved and that adoption be urged of a plan under which the federal government will provide for the wives of enlisted men a stated allotment for medical, hospital, maternity and infant care similar to the allotments already provided for the maintenance of dependents, leaving the actual arrangements with respect to fees to be fixed by mutual agreement with the wife and the physician of her choice. The reference committee at the same time disapproved the resolution from the state of New York because it involves the introduction of a third party—a party coming between the patient and the physician.

In his editorial Dr. Kress asks "Is it fair to a small group of constituent state medical associations to make them carry on this battle against governmental intrusion into the domain of private medical practice? On a subject of national scope, is it not to be expected that the national organization will point the way?" Certainly the detailed statement of Dr. Olin West sent to Dr. Kress, which Dr. Kress says will be placed in the files, indicates how definitely the national association has pointed the way, indicates how certainly the House of Delegate has acted in the matter, indicates finally that the editor of *California and Western Medicine* went to press with his periodical before he received sufficient factual information to warrant the statements that are made.

6. Sabin, A. B., and Ward, Robert: Science **98**: 300 (March 20) 1942.

1. Dr. Kress wrote to Dr. West on August 6; that letter was received in the office of Dr. West on August 9 at 8:23 in the morning and was answered by a letter sent on the afternoon of August 10. The communication written by Dr. Kress on August 17, received in the headquarters office on August 20 at 10:37 a. m., states: Dr. West's reply "was received too late to be of use in my August editorials for California and Western Medicine. I am very glad to have this information for *our files* [sic]."

2. California was allocated $20,000 during the first and second quarters of 1943 under the federal Social Security Act to be used for maternal and child health; sufficient maternal and child health funds were still available in the state for such services during the third quarter of 1943. Fifty thousand dollars was being requested by California for the fourth quarter of 1943.

Never before in the history of our country or of the world has there been such unrest as is now apparent among medical men and among some of the constituent state organizations of the American Medical Association. The unrest appears to be stimulated by fears related to proposed national legislation—such as the Wagner-Murray-Dingell bill, S. 1161—and efforts on the part of various agencies of the government to take over medical practice. Such efforts are not new; they have been persistent since 1928. During the fifteen years that have elapsed the maximum accomplishment in the way of legislation injurious to the quality of medical practice for the American people has been permissive legislation for some agencies of the government to utilize the services of osteopaths and some activities on the part of various government bureaus utilizing their own regulations, which have gone beyond the powers granted to them by the acts under which they operate.

The wives of enlisted men who need obstetric service should certainly be able to obtain good obstetric service and, when funds are not available, to receive aid for that purpose. This applies equally to the pediatric care necessary for the children of enlisted men. The service that these men render to the nation in offering their lives in its defense merits the most that the nation can give them. In many instances, no doubt, enlisted men are the possessors of considerable funds accumulated previously to their enlistment. In many instances, no doubt, these men married during the period of enlistment and their wives are still residents in the home of parents well able to care for their every need. In a proposed army of more than ten million men, however, those financially competent to this extent would probably constitute a minority. Moreover, those who are financially competent are not in the vast majority of cases availing themselves of the fees established by or the money provided by the federal Children's Bureau. They are now choosing, as they have in the past, the obstetrician and hospital of their choice, and they are paying the sums requested by such obstetricians for their services. Even this, however, should not weigh against the fundamental principle reiterated by the House of Delegates in the action taken at the meeting in June 1943. It was the belief of the House of Delegates that the funds available should be paid to the patient and that the matter of payment to be rendered was a matter for determination between the patient and the physician.

Notwithstanding these principles, many physicians and many state departments of health have accepted the proposals of the Children's Bureau and are giving obstetric and pediatric services in accordance with the plans that have been described. The medical societies of Michigan, Oregon, Ohio and California have recorded themselves as opposed to such plans.[3] The opposition, as stated by the Michigan State Medical Society, is based on the belief that this will encourage the development of a poor quality of obstetric and pediatric care, establish a precedent for further extension of governmental interest into the private practice of medicine, commit to such governmental activities those members of the medical profession who are in the military service and who have not had opportunity to express their opinions, and open the door to governmental medical service for all, without economic distinction or determination of need and establish a fee schedule. The real test of opposition to the program is the extent to which the individual physician will refuse to participate in its operation and the extent to which state medical organizations will express officially their unwillingness to approve. In this connection Dr. Daily concludes his article with this statement: "The cooperation of practicing physicians and hospital administrators, on whom much of the burden of the program ultimately rests, has made it possible for most of the state health agencies to establish these statewide services for the wives and infants of enlisted men in the armed forces."

3. A statesmanlike letter by the president of the Ohio State Medical Association, Dr. C. C. Sherburne, indicates that the whole subject was thrown into the political arena in Ohio, and this made the position of the medical profession most difficult.

Current Comment

ANTIBACTERIAL SUBSTANCES FROM ASPERGILLUS MOLDS

The remarkable effects of penicillin in certain bacterial infections have aroused interest in the production of antibacterial substances by fungi other than Penicillium notatum. Wiesner [1] found that strains of Aspergillus clavatus produced a substance which had bacterial as well as bacteriostatic effects on organisms not attacked by penicillin. Waksman and his associates [2] report the results of studies of antibiotic or antibacterial substances obtained from cultures of Aspergillus fumigatus and Aspergillus clavatus, isolated from soils, stable manure and composts. Grown in a glucose-nitrate medium A. fumigatus produces an extractable, crystallizable, antibacterial substance called fumigacin, which is active against gram positive bacteria but has only little effect on gram negative organisms or fungi. Aspergillus clavatus also produces an antibacterial substance on synthetic mediums. This substance is called clavacin. It differs from fumigacin both chemically and in its antibiotic actions, being almost as active against gram negative as against gram positive bacteria. It has not as yet been isolated in crystalline form. Only six of fifteen strains of A. clavatus produced clavacin in considerable amounts. Waksman and Schatz [2] caution against too hasty generalizations of the power of certain fungi to produce antibacterial substances based on the results of the study of single strains of a given fungus. Fumigacin and clavacin are notable

1. Wiesner, H. P.: Bactericidal Effects of Aspergillus Clavatus, Nature 149:356 (March 28) 1942.

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additions to the antibiotic agents derived from fungi. They differ in many respects from penicillin. Both "are fairly toxic to animals." Whether their selectively bacteriostatic and bactericidal properties can be used to advantage in treatment remains to be determined.

MERCURIALS AS "PRESERVATIVES"

In a recent study of protein sulfhydryl groups Hellerman, Chinard and Deitz [1] point out that organometallic compounds of the type R-Hg-X, such as phenylmercuric hydroxide and its derivatives, form poorly dissociated protein mercaptides by combination of the organic mercurial with protein thiol groups. According to Fildes [2] the formation of such mercaptides is the basis for the bacteriostatic action of mercury. Such sulfhydryl groups are present, however, not only in bacteria but in plasma and other proteins. Bacteriostatic action of such organomercuric compounds in the presence of serum is therefore largely prevented by competition of reactive groups on the serum proteins for the mercury. This presumably is the basis of the finding [3] that the "activity of a mercurial antiseptic in serum is reduced to 0.33-0.007 per cent of its activity in saline." Ignoring of these simple chemical facts can be responsible for very serious occurrences, such as the arrival in England of plasma "preserved" with 1:10,000 merthiolate containing viable micro-organisms. Johnson and Meleney [4] conclude:

> In our experience 1:10,000 merthiolate has not been able to insure the sterility of stored liquid plasma. The contaminations reported in this paper in plasma-saline mixture containing 1:10,000 merthiolate are sufficient to be an argument against its use. The material found to be contaminated when tested after its arrival in England is further evidence that 1:10,000 merthiolate cannot be considered the ideal preservative for plasma. Further research work in this field is indicated.

POLIOMYELITIC DEGENERATION OF MOTOR END PLATES

Cellular and vascular reactions in the central nervous system during the acute stages of poliomyelitis have been exhaustively studied. Report has not thus far been made, however, of the preceding or accompanying morphologic changes in the peripheral motor nerve endings and muscle fibers. To supply this deficiency, Carey [1] of the Department of Anatomy, Marquette University School of Medicine, has studied the microscopic changes in these peripheral structures. The results promise to be of clinical interest. Eight to twenty days after rhesus monkeys were inoculated intracerebrally with the Lansing strain of poliomyelitis virus (first to fourth day of paralysis) the animals were chloroformed; parts of each paralyzed muscle were fixed and stained with a modified gold method.[2] Carefully teased pieces of the impregnated muscles were photographed under low magnification, corresponding muscles from normal monkeys being used as controls. The photographs showed a 20 per cent reduction in the number of motor end plates by the first day of recognized paralysis, with residual end plates often retracted into ball-like masses or swollen and granular. By the second to fourth day approximately 50 per cent of the end plates had disappeared, with retraction of the completely denuded axis cylinders. The rates of degeneration were not equal in different parts of the same muscle, certain areas showing a total absence of motor end plates. During the early paralytic stages, masses of auriphilous inclusion bodies were present at the site of the original myoneural junction of many muscles. These ephemeral inclusion masses usually disappear by the seventh day of paralysis. The end plate studies are being continued on a larger series of experimental animals.

HYPOTRYPTOPHANIC STERILITY

Failure of farm animals to reproduce when placed on low protein diets [1] is of major economic interest. Study of the physiology of this nutritional sterility was facilitated when it was found that female rats placed on a low protein diet also would not reproduce.[2] Albanese and his colleagues [3] of Johns Hopkins University attribute this reproductive failure to an inadequate intake of certain amino acids. Normal adult male and female rats, for example, were reared on a stock diet and then mated. As soon as vaginal smears showed the presence of sperm, half of the females were segregated in individual cages and fed a tryptophan deficient diet ad libitum, an equal number of inseminated females being maintained as controls on the stock diet. After a gestation period of twenty-two to twenty-four days each normally fed control female gave birth to a litter of from 4 to 10 young (average 7 young). None of the inseminated females placed on the deficiency diet gave birth to young, the deficiency group showing a 100 per cent reproductive failure. A second group of inseminated females were killed on the ninth, eleventh, thirteenth and fourteenth days after being placed on the deficiency diet. Embryos of normal size and appearance were present on the ninth day, but by the fourteenth day almost complete resorption had taken place. From these experiments it would seem that tryptophan is an essential dietary factor for normal gestation in rats and that the available reserves of this amino acid in maternal tissues is depleted within ten days on a tryptophan deficient diet. Whether or not reproductive failure of domestic animals on low protein diet is due solely to tryptophan deficiency, however, has not yet been determined.

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4. Johnson, B. A., and Meleney, F. L.: Bacteriological Control of the Preparation of Plasma, in Blood Substitutes and Blood Transfusion, edited by Stuart Mudd and William Thalhimer, Springfield, Ill., Charles C Thomas, 1942, p. 263.
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MEDICINE AND THE WAR

In this section of The Journal each week will appear official notices by the Committee on War Participation of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medicine and the war, and such other information and announcements as will be useful to the medical profession.

ARMY

COLONEL JENSEN APPOINTED DEPUTY AIR SURGEON

Col. Walter S. Jensen of the Medical Corps has been appointed Deputy Air Surgeon of the Army Air Forces, Brig. Gen. David N. W. Grant, Air Surgeon, has announced. Colonel Jensen vacated the position of executive officer and was succeeded by Col. Henry C. Chenault, formerly chief, Professional Division, Air Surgeon's Office. Colonel Chenault's vacancy was taken by Lieut. Col. George L. Ball.

THE ETOUSA SOCIETY OF OPHTHALMOLOGY

The Etousa Society of Ophthalmology was conceived by United States Army ophthalmologists on the occasion of the British Congress of Ophthalmology. Under the direction of Lieut. Col. Derrick T. Vail, a preliminary meeting was held in the London Senior Officer's Mess on May 1 at which Brigadier Sir Stewart Duke-Elder was guest of honor. Plans were made for bimonthly meetings to be held at a different general hospital and it was decided to publish a bimonthly journal.

The first scientific meeting of the society was held at the Second General Hospital near Oxford, England, on July 10, attended by thirty American and two Canadian army officers, Lieut. Comdr. Edwin Dunphy of the Navy and one civilian, all ophthalmologists. The program arranged by Capt. F. P. Calhoun included five papers in the morning, the climax of which was "War Gas Injuries of the Eeyes" by Lieutenant Commander Dunphy. In the afternoon there were exhibits of photographs, drawings and movies with the presentation of 8 cases. The meeting ended with a dinner-dance given by the nurses. The next meeting will be held at the Fifth General Hospital in September.

PHARMACY CORPS ESTABLISHED IN MEDICAL DEPARTMENT

The Seventy-Eighth Congress passed Public Law No. 130 establishing a Pharmacy Corps in the Medical Department of the Army to consist of seventy-two officers in grades from colonel to second lieutenant. Appointments in the Pharmacy Corps will be made in the grades of second lieutenant from pharmacists between 21 and 32 years of age who are graduates of recognized pharmacy schools requiring four years of instruction, under such regulations as the Secretary of War shall prescribe. Officers of the Pharmacy Corps will be promoted to first lieutenant after three years' service, to captain after six years' service, to major after twelve years' service, to lieutenant colonel after twenty years' service and to colonel after twenty-six years' service, provided officers in the Regular Army holding commissions in the Medical Administrative Corps on the date this law was enacted shall be transferred to the Pharmacy Corps and commissioned in grade in that corps in addition to the seventy-two officers authorized for the Pharmacy Corps. The act was approved on July 12.

AVIATION PHYSIOLOGISTS

A routine course of instruction for aviation physiologists began on August 2 at the School of Aviation Medicine, Randolph Field, Texas. Among the students enrolled are First Lieuts. Aaron Grossman, Morton McMichael, Emanuel Marcus and Frederick S. Spiegel.

MORE PHYSICAL THERAPY AIDES WANTED

Physical therapy aides are now serving in 140 army hospitals in the United States and in 32 overseas. The administration of physical therapy requires knowledge of anatomy, physiology and pathology. It includes treatment by means of massage, exercise, electricity, water and various forms of heat. The Medical Department has expanded its training program so that student physical therapy aides are being trained at Walter Reed General Hospital, Washington, D. C.; Fitzsimons General Hospital, Denver; Brooke General Hospital, Fort Sam Houston, Texas; Army and Navy General Hospital, Hot Springs, Ark., and O'Reilly General Hospital, Springfield, Mo. Over twenty civilian institutions are also cooperating in training physical therapy aides. Many of these courses have been intensified and reduced to courses of six months' duration to meet the emergepcy. Civilian hospitals conducting such courses are Children's Hospital, Los Angeles; College of Medical Evangelists, Los Angeles; University of California Hospital, San Francisco; Stanford University, Palo Alto, Calif.; Northwestern University Medical School, Chicago; State University of Iowa Medical School, Iowa City; Bouve-Boston School of Physical Education, Boston; Harvard Medical School, Cambridge, Mass.; Boston University-Sargent College of Physical Education, Boston; University of Minnesota, Minneapolis; Mayo Clinic, Rochester, Minn.; Barnes Hospital, St. Louis; St. Louis University School of Nursing, St. Louis; University of Buffalo School of Nursing, Buffalo; Hospital for Special Surgery, New York; New York University, New York; Cleveland Clinic Foundation Hospital, Cleveland; D. T. Watson School of Physio-Therapy, Leetsdale, Pa.; Graduate Hospital of the University of Pennsylvania, Philadelphia; Richmond Professional Institute, Richmond, Va.; University of Wisconsin Medical School, Madison.

To be eligible for appointment as a Medical Department physical therapy aide on a military status an applicant must have completed two years in an approved college with emphasis on physical education or biologic science, or graduated from an accredited course in nursing; and, in addition to one of the foregoing, completed a training course in physical therapy approved by the Surgeon General. She must be at least 5 feet tall and weigh 105 pounds, must not have passed her 45th birthday, must be a citizen of the United States or of a cobelligerent or friendly country, must meet the physical requirements as prescribed in Army Regulations and have no dependent children under 14 years of age.

Current Army needs are for 1,000 additional trained physical therapy aides. They are being recruited through the Officer Procurement Service, located in each of the nine service commands of the Army and in the large cities.

On Dec. 22, 1942 the President signed Public Law No. 828, which brought physical therapy aides into the Army on the same basis as Army nurses. Under the act the aides receive an initial issue of clothing, including six regulation white uniforms and caps, a woolen street uniform, woolen cape, shoes, purse and other articles. The only difference in the appearance of Army nurses and physical therapy aides is in the insignia worn. Army nurses have the letter N on the caduceus while physical therapy aides have the letter PT on the caduceus.

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NAVY

NEW DISPENSARY HOSPITAL UNITS

The Bureau of Medicine and Surgery of the Navy has announced that new dispensary hospital units have been completed at six auxiliary airfields in Florida, each containing ward facilities for 42 patients, x-ray equipment, complete laboratory facilities, flight surgeons' instruments, examining room and the usual medical, surgical and pharmacy facilities. Three medical and two dental officers will be assigned to each unit.

ISLAND NATIVES GIVE TO RED CROSS

Forty-four chiefs and headmen of native tribes on an island in the Solomon Islands have contributed $194.62 to the American Red Cross, the money having been forwarded through the Navy, which has a base on the island. The natives have been treated on a voluntary basis in cases of illness or injury by navy medical officers and exhibit a friendly feeling toward America. Lieut. E. V. Best, Chaplain Corps, U.S.N.R., Conway, S. C., presented the check for $194.62 to Mr. John Carney, director of the American Red Cross for the South Pacific Area.

MEDICAL KITS FOR PATROL BOATS AND SUBMARINE CHASERS

The Medical and Surgical Relief Committee of America, 420 Lexington Avenue, New York, had on August 16 completed the second round of shipments of emergency medical kits to the thirteen naval districts of the Coast Guard for use on patrol boats. The committee has to date distributed three hundred and sixty-two patrol boat sets to the Coast Guard and has donated one hundred and ninety-one similar medical kits to Navy submarine chasers, sending them directly to the commanding officer of the individual ships.

The submarine chaser or patrol boat medical kit is a compact case containing essential drugs and instruments and was especially designed by committee physicians to provide emergency treatment to casualties until the ship reaches a base hospital. The kit has proved to be particularly useful when patrol boats pick up shipwreck survivors.

The Medical and Surgical Relief Committee, which is celebrating its third birthday, is conducted by a nationwide group of physicians for the purpose of sending medical aid to the armed and civilian forces of America and her allies; so far the committee has donated $562,000 worth of medicines, vitamins, surgical equipment and other supplies to military units, needy hospitals, welfare agencies in the war zone and civilian defense posts.

NAVY PROMOTIONS

The following officers have been promoted to captain (MC), U.S.N.:

Paul T. Crosby
Raymond B. Storch
Robert E. S. Kelley
Enoch R. Brian
Emil J. Stelter
Harry J. Scholtes
Herbert L. Pugh
Oliver A. Smith
Edward P. Kunkel
E. M. Harris Jr.
Winfred P. Danna
Robert M. Gillett
Henry D. Templeton
Dwight J. Wharton
Arthur P. Morton
Harvey E. Robins
John W. Owsley
Arra B. Chesser
Lloyd R. Newhouser
Thomas F. Cooper
Carl M. Dumbauld
Walter F. J. Karbach

The following officers have been promoted to commander (MC), U.S.N.:

Charles L. Ferguson
Cecil H. Coggins
Walter H. Schwartz
Alfred W. Eyer (detached)
James B. Butler
Charles D. Bell
Alton R. Higgins

POSTHUMOUS AWARD TO LIEUT. MILES

The President of the United States on August 5 awarded the Silver Star Medal posthumously to Lieut. (jg) Samuel S. Miles (MC), U.S.N.R., for service as set forth in the following citation:

For conspicuous gallantry and intrepidity while attached to Headquarters Company, First Marine Raider Battalion, during the attack on enemy Japanese forces on Tulagi, Solomon Islands, on Aug. 7, 1942. Knowing that three men of another company had been killed and numerous others wounded, Lieutenant Miles, with utter disregard for his own personal safety, attempted to cross a zone swept by hostile fire in order to administer first aid to the wounded and isolated men and was killed by the enemy. His great personal valor and heroic devotion to duty were in keeping with the highest traditions of the United States Naval Service. He gallantly gave up his life in the defense of his country.

NAVY PERSONALS

Lieut. Comdr. Charles F. Gell has reported to the Bureau of Medicine and Surgery and has been assigned for duty to the Bureau of Aeronautics in the Navy Department.

Capt. Fred W. Muller and Lieuts. Martin Buehler and Evan C. Stone reported for duty at the Bureau of Medicine and Surgery, Washington, D. C., in June.

Lieut. Comdr. Charles Wheatley (MC), U.S.N., Ret., has been promoted to the rank of commander on the retired list.

CIVILIAN DEFENSE

SHORT COURSES IN OREGON ON CHEMICAL WARFARE

The Oregon State Medical Society, University of Oregon Medical School and Oregon State Defense Council jointly are sponsoring a series of short courses to assist physicians of the state in keeping informed on the latest medical aspects of chemical warfare, especially as it pertains to civilians. These courses have been or will be given in Portland, Marshfield, Salem, Eugene and Astoria. Among the subjects of lectures were the symptoms and treatment of lacrimators, sternutators, systemic poisons and lung irritants and the symptoms, physiology, pathology and treatment of vesicants. The lecturers were Edward S. West, Ph.D., Charles W. Wilson, M.D., Charles E. Gurney, M.D., all of the University of Oregon Medical School, and Vernon A. Douglas, M.D., director of the Emergency Medical Service, Oregon State Defense Council. While some of the initial series of these courses have already been finished, the course at Salem will be given at 6:30 p. m. July 30 and at Eugene August 13, at Astoria August 20 and at Portland September 27. Additional information can be obtained from the Oregon State Medical Society, Medical-Dental Building, Portland, Oregon.

APPOINTMENT OF NEW REGIONAL MEDICAL OFFICERS

The Office of Civilian Defense, Washington, D. C., announced on August 9 the appointment of Dr. Harrison A. Walker, Miami Beach, Fla., as regional medical officer in the Fourth Civilian Defense Region, with headquarters in Atlanta, to succeed Dr. Burt A. Dyar, who is now living in Custer, S. D. Dr. Walker graduated from Indiana University School of Medicine in 1917 and later was an instructor in surgery at his alma mater. Since 1925 he has practiced in Florida, where he was a member of the surgical staffs of the James M. Jackson Memorial Hospital in Miami and the St. Francis Hospital in Miami Beach.

Dr. Ozro T. Woods, Dallas, Texas, has been appointed regional medical officer of the Eighth Civilian Defense Region to succeed Dr. Witten B. Russ. Dr. Woods graduated from the University of Nebraska College of Medicine in 1924, since which time he has been a member of the faculty of Baylor University School of Medicine in Dallas, where since 1928 he has been associated with the Dallas Medical and Surgical Clinic.

UNIFORMS OF U. S. CADET NURSE CORPS

A Molly Parnis wardrobe was selected as the official street uniform of the U. S. Cadet Nurse Corps by a jury of thirty-two fashion editors of national magazines, newspapers, radio and movies at a luncheon sponsored by the National Nursing Council for War Service at the Waldorf Astoria in New York City on August 16. The winning entrant consists of wool suit, top coat, striped cotton summer suit, raincoat and round necked blouses, to be worn with a beret modeled after that of General Montgomery. The basic color is a soft dark gray.

The official insignia of the U. S. Public Health Service will be worn by the U. S. Cadet Nurse Corps. The cap device consists of the fouled anchor (denoting distress) of the Navy Medical Corps and the caduceus of the Army Medical Corps, crossed behind the American shield and surmounted by a spread eagle. Buttons and lapel ornaments carry the crossed anchor and caduceus. These insignia were first adopted in 1798. The Maltese cross will be worn on the upper left sleeve of the cadet nurse corps uniform. The Maltese cross, historically associated with the profession of nursing since it was worn by the Knights Hospitalers in the first crusade, is silver against a dark red background.

Assurance that women in essential industries will be released for the United States Cadet Nurse Corps, just as they are for WAC, WAVES, SPARS and Woman Marines, was brought

Insignia of the United States Public Health Service to be worn by members of the U. S. Cadet Nurse Corps on the beret, the sleeve and the lapel.

the guests by Dr. Parran from the director of the War Manpower Commission. Other guests were Mrs. Frances P. Bolton, Congresswoman from Ohio; Miss Sophie Nelson, vice chairman of the National Nursing Council for War Service; Miss Lucile Petry, director, U. S. Cadet Nurse Corps; Asst. Surg. Gen. Charles C. Hillman, Army Medical Corps; Mrs. Herbert H. Lehman, Federal Security Agency; Rear Admiral K. C. Mellhorn of the Navy; Col. Florence A. Blanchfield, superintendent of the Army Nurse Corps, and Dr. George Baehr, chief medical officer, Office of Civilian Defense.

FREE TRAINING FOR NURSES

Allotments totaling $836,461 to six nursing schools offering free nurse training in conjunction with the program of the U. S. Cadet Nurse Corps were approved on August 16 by Dr. Thomas Parran, Surgeon General, U. S. Public Health Service. The funds will be used to accelerate the training of nurses for essential civilian and military service during the war emergency. Students receive tuition, fees, stipends and uniforms from these allocations.

The schools to which funds were allotted include:

Children's Hospital School of Nursing, Boston, $44,960, affecting about 64 nurses in training and 25 to enroll.

Bridgeport Hospital School of Nursing, Bridgeport, Conn., $88,436, affecting about 80 nurses in training and 80 to enroll.

Christ Hospital School of Nursing, Cincinnati, $144,068, affecting about 124 nurses in training and 128 to enroll.

Highland School of Nursing, Oakland, Calif., $161,754, affecting about 171 nurses in training and 80 to enroll.

Presentation School of Nursing in four units, with headquarters at Aberdeen, S. D., and units at Sioux Falls and Mitchell, also in South Dakota and Miles City, Mont., $280,459, affecting about 278 nurses in training and 115 to enroll.

Cook County School of Nursing, Chicago, $116,784, affecting about 96 nurses in training and 130 to enroll.

The program of the United States Cadet Nurse Corps was approved at the last session of Congress, and its objective is to enroll 65,000 student nurses immediately.

CEILING PRICES FOR SYNTHETIC RUBBER DRUG SUNDRIES

As hot water bottles and combination syringes made of synthetic rubber for use in hospitals have been coming on the retail market for the first time, the Office of Price Administration on August 12 gave them retail selling prices in line with the prewar prices for the same grade when made of crude rubber.

Today's maximum retail price for the Victory line hospital grade molded hot water bottles made of synthetic rubber is $1.30; retail ceilings for two lower grades, which were in the regulation already, are $1 and 75 cents respectively. The retail ceilings for three types of the Victory line hospital grade combination syringes range from $1.65 to $2.20. Combination syringes of the lower grade, already priced in the regulation, range from $1.10 to $1.90. No price increase is represented by the ceilings set for the hospital grade on sales in the retail market because they are at the same level that existed before the war for sales of the same grade when made of crude rubber; these prices have always been above those for hot water bottles and combination syringes of lower grades. The hospital grade is made to more stringent specifications and is more durable than those grades not made especially for use in hospitals.

This amendment became effective on August 19.

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ORGANIZATION SECTION

OFFICIAL NOTES

WAR PARTICIPATION COMMITTEE

Meeting held in Washington, D. C., July 30-31

Present: Members: Drs. Edward R. Cunniffe, Walter F. Donaldson, chairman, Morris Fishbein, William R. Molony and James E. Paullin; also Dr. Roscoe L. Sensenich and Lieut. Col. Harold C. Lueth.

Questions introduced for discussion were:

Are present methods of obtaining medical personnel the best that can be devised?

The Procurement and Assignment Service for Physicians, Dentists and Veterinarians is in need of aid in securing replacements in civilian areas.

Since it is reported that some 1,600 physicians have been discharged from the armed forces, are present methods of utilizing physicians discharged from the service satisfactory?

What will be the effect of the present Army and Navy specialized training program on the future of medical education?

Is the Army utilizing physicians to the best advantage?

It was decided that the latter two questions should be introduced at the joint session with the Directing Board of Procurement and Assignment Service and the Surgeon Generals of the Army, Navy and Public Health Service; also a request for clarification of the order covering men between the ages of 38 to 44 recently issued by the Adjutant General's Office.

Other questions to be raised were agreed on as follows:

A. What pressures may be agreed on toward encouraging recruitment of medical officers?

B. What are the current standards of "essentiality" and "availability"?

C. Can recruitment be encouraged by further modifying the physical requirements?

D. Is there any hope of gaining additional recruits through physical rehabilitation?

E. What is the status of men now classified as "essential in research"?

Formal action was taken by which the War Participation Committee requests the Board of Trustees of the American Medical Association to recommend to the Association's Postwar Planning Committee the development of plans for (1) continuing education, including internship, residencies and refresher courses for physicians discharged from the armed forces, also (2) consideration to be given to the relocation of physicians emerging from the armed forces and such other aid as may be given to ex-service physicians on request. It was suggested that the Postwar Planning Committee submit its program for these purposes to the next meeting of the House of Delegates.

Subsequently the committee also decided to submit to the Board of Trustees of the American Medical Association for appropriate action the following:

That the American Medical Association ask the state and local medical societies to cooperate with the Procurement and Assignment Service in carrying out its obligations to the armed forces and the civilian population in procuring more physicians for the armed forces and effecting a better distribution of physicians.

That the Board of Trustees of the American Medical Association utilize the activities of that association, such as THE JOURNAL and other divisions, in this program.

The committee met at 9 a. m. at the Hotel Statler. Present were Drs. Edward R. Cunniffe, Walter F. Donaldson, chairman, Morris Fishbein, Roger I. Lee, William B. Molony and Olin West.

The committee reviewed the agenda that had been prepared at the session of the previous evening and approved its presentation to the Directing Board of the Procurement and Assignment Service for Physicians, Dentists and Veterinarians.

Following extended discussion, the committee adjourned to meet at 11 a. m. with the Directing Board of the Procurement and Assignment Service and with representatives of the Offices of the Surgeon Generals of the Army, Navy and Public Health Service, and the Officer Procurement Service in the New Social Security Building.

The War Participation Committee offered the full cooperation of the American Medical Association in aiding the procurement of some 5,000 to 6,000 additional physicians required to meet quotas up to Jan. 1, 1944. Ways and means were discussed for aiding the recruitment of physicians in various areas.

During the afternoon joint session a statement was made by the Hon. Paul V. McNutt, chairman of the War Manpower Commission, relative to the needs for physicians. Mr. McNutt expressed his appreciation of the work of the Directing Board of the Procurement and Assignment Service and of the American Medical Association. He felt that the medical profession was the only group authorized to conduct its own recruitment and the safeguarding of professional services in civilian life and that the task had been well done. He discussed also proposals for aiding the procurement of physicians during the remainder of the year as well as many of the questions prepared by the Committee on War Participation.

OBSTETRIC AND PEDIATRIC CARE FOR WIVES AND CHILDREN OF ENLISTED MEN

[*See editorial, this issue, page 1251.*]

[Letter sent by Dr. George H. Kress, secretary-editor, California Medical Association, Aug. 6, 1943:]

Dear Doctor West:

We continue to be much interested in the Federal Children's Bureau Plan.

We have noted the following articles in THE JOURNAL:

Maternity Care for Wives of Enlisted Men, THE JOURNAL, July 17, p. 816.
Daily, E. F.: Medical and Hospital Maternity and Infant Care, *ibid.*, July 31, p. 945.

I am writing to ask if any other articles appeared in THE JOURNAL on the subject, and if so, will you kindly send me the references?

Thanking you for your prompt attention to this,

Cordially yours,
GEORGE H. KRESS, M.D., San Francisco.

[Reply of Dr. Olin West, Secretary, American Medical Association, sent August 10:]

Dear Doctor Kress:

Your letter of August 6 was received on August 9, since which time I have had prepared a list of references to items pertaining to obstetric and pediatric care for the wives and children of service men that have appeared in THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

I presume you know that the program of the Children's Bureau for providing obstetric service was initiated in the state of Washington in 1941 and was extended to other states beginning in August 1942.

In the Federal Legislative Bulletin No. 19 of our Bureau of Legal Medicine and Legislation, dated Sept. 1, 1942, there was a three page discussion of legislation introduced at the request of the President of the United States proposing an additional appropriation for the Children's Bureau. Part of this appropriation was to be used to provide maternity services for the wives of service men. This bulletin was sent to the officers of all state medical associations.

On page 47 of THE JOURNAL for Sept. 5, 1942 there appeared an editorial comment on the two bills that had been introduced at the request of the President. It was pointed out in the editorial comment that part of the appropriation provided for in the bills was to be used for maternity care for the wives of service men. In the same issue of THE JOURNAL, on page 58,

there was a brief reference to the introduction of these two bills, neither of which was enacted.

In THE JOURNAL for Nov. 14, 1942 on page 846 there was an item under the title "Medical Care for Wives and Infants of Men in Military Service" in which reference was made to the program of the Children's Bureau and to the fact that funds had been set aside by the bureau from its appropriation for the fiscal year 1943 in the amount of $198,000.

In THE JOURNAL for Nov. 21, 1942 on page 974 there was a news item descriptive of the plan being put into operation in the state of Missouri for providing medical and hospital obstetric and pediatric care for the families of men serving in the armed forces.

On page 603 of THE JOURNAL for Feb. 20, 1943 reference was made to a supplemental estimate that had been submitted to the Seventy-Seventh Congress by the President asking for an appropriation of $1,200,000 to be used by the Children's Bureau in making grants to states to provide medical, nursing and hospital maternity and infant care for wives and babies of enlisted men of certain grades serving in the armed forces. In the Federal Legislative Bulletin No. 25, dated March 1, 1943 reference was made to this supplemental estimate that had been submitted to Congress and to the fact that the House Committee on Appropriations had refused to include the estimate in the deficiency appropriation bill, H. R. 1975.

On page 872 of THE JOURNAL for March 13, 1943 reference was made to a bill introduced by Representative Keefe, H. R. 2041, proposing to authorize an appropriation of $6,000,000 for each fiscal year during the war and for six months thereafter to provide obstetric and pediatric care for the wives and infants of service men. This bill, as I am informed, is still in the hands of the House Committee on Education and Labor.

In the Federal Legislative Bulletin No. 25, dated April 5, 1943 reference was made to the fact that when the deficiency appropriation bill, H. R. 1975, came before the Senate for consideration there was included in the bill the appropriation requested by the President, and that the House thereafter agreed to this appropriation and the President signed the bill. In this same issue of the Bulletin reference was made to the bill introduced by Representative Keefe.

On page 1231 of THE JOURNAL for April 10, 1943 there was an item under the heading "Medical Care for the Wives and Children of Enlisted Men" which referred to the appropriation of $1,200,000 that had been made available for obstetric and pediatric services, to the regulations that had been promulgated by the Department of Labor under date of March 26 for the allotment of this money and to the nature of the testimony given by the chief of the Children's Bureau before a subcommittee of the House Committee on Appropriations in support of the request for the appropriation.

On page 1379 of THE JOURNAL for April 24, 1943 there appeared in the Report of the Board of Trustees a reference to the federal program here under discussion.

On page 382 of THE JOURNAL for June 5, 1943 there was an item under the title "Maternity Care for Wives of Certain Grades of Enlisted Men" summarizing the extent to which the plan had been put into operation.

There appeared in THE JOURNAL for June 26, 1943 on page 628 a reference to H. R. 2935, the Labor Department-Federal Security Agency appropriation bill for the fiscal year ending June 30, 1944, which contained at that time provision for the appropriation of $4,000,000 for the use of the Children's Bureau in carrying out the program under discussion. This sum was increased before the appropriation bill was enacted to $4,400,000.

On page 621 of the same issue of THE JOURNAL reference was made to the action taken by the House of Delegates of the American Medical Association in approving generally the action of the federal government in making funds available for maternity and infant care for the wives and infants of enlisted men but recommending that allotments be paid directly to the wives.

In the Federal Legislative Bulletin No. 28 under date of July 15, 1943 reference was made to the enactment of the Labor Department-Federal Security Agency appropriation bill authorizing the appropriation of $4,400,000 for grants to states to provide obstetric and pediatric care.

On page 816 of THE JOURNAL for July 17, 1943 there appeared a statement which was in the nature of a summary of the report issued by the Secretary of Labor on the progress made in the several states in carrying out the program of the Children's Bureau.

In THE JOURNAL for July 31, 1943, beginning on page 945, there appeared a special article by Dr. Edwin F. Daily, director of the Division of Health Services of the Children's Bureau.

There have been other references in special legislative bulletins sent to all state medical associations by our Bureau of Legal Medicine and Legislation pertaining to the proviso included in the appropriations bill H. R. 2935 which places certain restrictions on the Children's Bureau.

There seems to have developed an impression on the part of many that the plans of the Children's Bureau for providing obstetric and pediatric services for the wives and infants of enlisted men were not initiated until March 18, 1943, on which date the President signed the deficiency appropriation bill in which was included provision for the appropriation of $1,200,000 to finance the program of the Children's Bureau for the remainder of the fiscal year. The fact is that the program of the Children's Bureau was initiated in 1941 after the department of health of the state of Washington had petitioned the Children's Bureau for financial assistance to help in providing obstetric and pediatric service for the wives and children of enlisted men stationed at Fort Lewis. That was the first project started, and no other similar project was put into operation until August 1942. In the time between August 1942 and February 1943, programs quite similar to the one initiated in the state of Washington became effective in twenty-seven states, and the Children's Bureau made available the sum of $390,177 to be used in financing the programs in those states. These funds were set aside by the bureau from the regular appropriation authorized for maternal and child health services under part 1 of title V of the Social Security Act. Our information is to the effect that other states than the twenty-seven referred to made application for funds to be similarly used, which could not be granted because the bureau had no additional funds available.

In view of the fact that at least twenty-seven states collaborated in the program of the Children's Bureau over a considerable period of time, it is a little surprising that no state medical association found the program so objectionable as to induce the filing of any complaints with the American Medical Association. I have heard that the program was approved in some states, though I have no official advices to that effect. However, articles appeared in some state medical journals that were entirely favorable to the bureau program. In the *Journal of the Medical Society of New Jersey* for November 1942 there appeared a two page statement in which it was stated that the Medical Society of New Jersey had agreed to participate in the program and the reasons for that decision were given. A somewhat similar statement appeared in the *Journal of the Missouri State Medical Association* for November 1942.

I presume that by this time you have received a release from our Bureau of Legal Medicine and Legislation pertaining to the opinion of the Attorney General of the United States with respect to the effect of the provisos that were included in the appropriation bill for the Department of Labor, of which the Children's Bureau is a part.

It will no doubt interest you to know that I had a visit a few days ago from the health officer of one of our larger Middle West states, who stated that applications for obstetric and pediatric service for the wives and children of soldiers were coming into his office at the rate of one thousand a month and that the tentative estimate indicated that the cost of such service in that one state under the Children's Bureau program probably would amount to $1,250,000 a year. In that particular state, I understand, the fee for obstetric service including antepartum and postpartum care will be fixed at $45. Our visitor made a very interesting point when he stated that in many if not in most instances the wives of soldiers demand that they have the services of the best qualified obstetricians, who are already overwhelmed with work, and he expressed a fear that the obstetricians would be put in a bad light if they refused to serve the wives of soldiers under the Children's Bureau-State Health Department program even though their own private practice demanded every minute of their time.

If this service is to cost a million and a quarter in one state, the appropriation of $4,400,000 will be exhausted very rapidly.

With most cordial good wishes, I am

Very sincerely yours,

OLIN WEST.

[Letter from Dr. George H. Kress, secretary-editor, California Medical Association, sent Aug. 17, 1943:]

Dear Doctor West:

Many thanks for your courtesy in sending to me your letter of August 10 with its information concerning references in THE JOURNAL on maternity-pediatric care.

The letter was received too late to be of use in my August editorials for *California and Western Medicine*.

I am very glad to have this information for our files.

Cordially yours,

GEORGE H. KRESS, M.D., Secretary-Editor.

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

COLORADO

First Case of Typhus.—On July 3 a Denver physician reported a case of typhus. According to the Colorado State Board of Health *Bulletin*, this is the first instance on record in which typhus has occurred in Colorado. The patient was a man who has been a long time resident of Denver with a history of not leaving the city for a considerable period of time.

University News.—Dr. Lloyd J. Florio, associate professor of public health and laboratory diagnosis, University of Colorado School of Medicine, Denver, has been granted a leave of absence to study tropical medicine in Central America under a grant from the Markle Foundation, newspapers reported on June 2. Drs. John M. Lyon and Robert W. Davis have been appointed assistant professors of psychiatry at the school and Dr. Merrill C. Jobe named assistant professor of surgery, all of Denver.

FLORIDA

Annual Graduate Course.—The eleventh annual graduate short course for physicians was held in Jacksonville, June 21-26, under the auspices of the state medical association. The instructors were:

Dr. Robert W. Wilkins, Boston, Medicine.
Dr. Alton Ochsner, New Orleans, Surgery.
Dr. Samuel F. Ravenel, Greensboro, N. C., Pediatrics.
Dr. M. Pierce Rucker, Richmond, Va., Obstetrics.
Dr. Clayton T. Beecham, Philadelphia, Gynecology.
Dr. Austin V. Deibert, Hot Springs National Park, Ark., Venereal Diseases.

IDAHO

Hospital News.—Plans are being considered to turn over to the Army and Navy the partly completed state tuberculosis hospital at Gooding.

State Medical Meeting.—The fifty-first annual meeting of the Idaho State Medical Association will be held at the Owyhee Hotel, Boise, August 30-31. The tentative program includes the following speakers:

Lieut. Col. Frank B. Queen, National Guard, Penicillin; Laboratory Diagnosis of Tropical Diseases.
Lieut. Col. James S. Sweeney, M. C., A. U. S., Clinical Interpretation of Blood Pressure; Peptic Ulcer Syndrome.
Lieut. Col. Henry G. Hollenberg, M. C., A. U. S., Recent Advances in Vascular Surgery; The Acute Surgical Abdomen.
Major Max T. C. Schnitker, M. C., A. U. S., Diagnosis and Treatment of Acute Head Injuries and Peripheral Injuries.
Major Ernest E. Myers, M. C., A. U. S., Pitfalls in Treatment of Fractures; Amputations.
Lieut. Col. Olin B. Chamberlain, M. C., A. U. S., Concepts of Psychosomatic Medicine; Acute Episodes Simulating Psychoses.

ILLINOIS

New Species of Mosquito Found in State.—Among more than 200,000 mosquitoes collected and identified by sanitary engineers and entomologists connected with Illinois projects for malaria control in war areas there were found four species that had never been known to exist in the state. According to the *Illinois Health Messenger*, among them was Aedes aegypti, the species that transmits yellow fever.

Chicago

Course in Otolaryngology.—The department of otolaryngology of the University of Illinois College of Medicine will conduct the second of its series of short refresher courses, the program to include one week of didactic instruction, September 27-October 2, and three days of clinical conferences, October 4-6. The fee for the course will be $50. Registration will be by application through the department of otolaryngology at the medical school.

Grant for Research in Penicillin.—The Schenley Distillers Corporation through its president, Louis Rosenstiel, has made available to Northwestern University Medical School a grant for research on penicillin to include the production of the product and its application in cases of disease. A special committee has been established to control this research. The committee includes Chester J. Farmer, M.A., chairman, Dr. Alexander A. Day, Dr. Sumner L. Koch, Dr. Walter S. Priest, Henry B. Bull, Ph.D., Dr. Guy P. Youmans and Mr. Samuel E. Thomason.

New Pharmacology Department at Loyola.—With the appointment of Dr. Amedeo S. Marrazzi, assistant professor of pharmacology, New York University College of Medicine, effective September 1, as professor and head of the department of pharmacology, a new pharmacologic unit will be launched at Loyola University School of Medicine. Pharmacology and the department of physiology have been operating under the direction of Dr. Theodore Boyd, who under the new arrangement will continue as professor and head of the department of physiology. Dr. Edward Piszczek, health commissioner of Cook County, has been made acting chairman of the department of bacteriology and public health.

KANSAS

Personal.—Dr. Samuel N. Mallison, El Dorado, has resigned as health officer of Butler County to become superintendent of the Southern Illinois Health District with offices in Harrisburg, Ill.——Dr. William T. Grove, Eureka, has been appointed health officer of Greenwood County to succeed Dr. Walter S. Moonlight, Eureka, resigned.——Dr. Charles W. Jones, Olathe, has been appointed a member of the state board of medical registration and examination to succeed Dr. James E. Hanshall, Osborne.

Courses on Lung Disease.—On August 28 a postgraduate course in lung disease will start in Kansas City under the auspices of the University of Kansas School of Medicine, Lawrence-Kansas City, the state board of health, the Kansas Tuberculosis and Health Association and the state medical society. The program will be offered in Parsons on August 30, Wichita September 1, Salina September 2 and Emporia September 4. Three sessions will be held in each town. Drs. Carl C. Birkelo, Detroit, and Henry C. Sweany, Chicago, will be the instructors.

KENTUCKY

Rocky Mountain Spotted Fever.—One death from Rocky Mountain spotted fever occurred in Bracken County early in August, newspapers report. In the last three years 3 cases of the disease have appeared in the county, all in children, 2 of which were fatal.

LOUISIANA

Dr. Trufant III Wins Walter Reed Award.—Dr. Samuel Adams Trufant III, who graduated this year at the Tulane University of Louisiana School of Medicine, New Orleans, has been presented with the Walter Reed Memorial Award for his thesis entitled "Sylvatic Plague." The award is given by the Louisiana State Medical Society to a senior student at Tulane or the University of Louisiana School of Medicine. Ultimately a medal will signify the award but thus far, since the first presentation in 1942, the prize has been represented by a certificate of award.

Dr. Duncan Named Professor of Anatomy.—Donald Duncan, Ph.D., professor and head of the department of anatomy at the University of Buffalo School of Medicine, Buffalo, has been appointed professor of anatomy at Louisiana State University School of Medicine, New Orleans. Dr. Duncan received his Ph.D. at the University of Minnesota, Minneapolis, in 1929. Later he served for a time at the University of Utah, Salt Lake, as assistant professor of anatomy and at the University of Texas Medical Branch, Galveston, as associate professor of anatomy. His appointment to the Louisiana faculty will take effect on October 1.

MAINE

Personal.—Dr. Emanuel Levy, chief of the medical service of the Veterans Administration Facility, Bronx, N. Y., has been appointed chief medical officer at the Veterans Administration Facility in Togus.

Medicolegal Officers Named.—New officers of the Maine Medico-Legal Society, elected at the annual meeting in Augusta June 20, are Dr. Delbert M. Stewart, South Paris, president; Benjamin Butler, Farmington, vice president; Dr. George L. Pratt, Farmington, secretary, and Dr. Walter S. Stinchfield, Skowhegan, treasurer.

MASSACHUSETTS

Bequest for Hospital Laboratories.—Brooks Hospital, Brookline, will receive $300,000 and the residue of the estate for the maintenance of its laboratories through a provision in the will of the late Mrs. Alice E. Sias, Boston. The hospital will also receive $25,000 for general use. The bequest for the laboratories, which were established by Mrs. Sias several years ago as a memorial to her husband, will be set up in a trust fund.

Dr. Hale Retires at Harvard.—Dr. William Worth Hale, since 1918 associate professor of pharmacology and assistant dean of the faculty of medicine, Harvard University, Boston, will retire from his teaching activities at the university on August 31. Dr. Hale, who graduated at the University of Michigan Medical School, Ann Arbor, in 1904, served for a time as assistant surgeon with the Granite Mining Hospital, Montana, assistant in pharmacology at the University of Michigan and from 1908 to 1913 as assistant pharmacologist with the U. S. Public Health Service. He joined the faculty of medicine at Harvard in 1913 as assistant professor of pharmacology. He will continue as assistant dean of the faculty of medicine and chairman of the committee on admissions. This spring students of the graduating class dedicated their yearbook "The 1943 Aesculapiad" to Dr. Hale.

MICHIGAN

Chapter of Soviet Medical Society.—The Detroit chapter of the American-Soviet Medical Society was launched at a meeting, August 18, at which Dr. Vladimir V. Lebedenko of the department of surgery, First Moscow Medical Institute, was the principal speaker, discussing his experiences with Soviet war medicine. Dr. Warren B. Cooksey, head of the Michigan Blood Bank, presided. The American-Soviet Medical Society was recently organized to stimulate the exchange of medical information between the United States and the Soviet Union (THE JOURNAL, June 12, p. 457).

Society Asked to Curb Advertising Clinics.—A drive to stamp out advertising clinics, sanatoriums and such like which profess to be able to "cure everything, but which in reality are nothing but unadulterated fakers," was announced on July 3 by George F. Addes, secretary-treasurer of the U. A. W.-C. I. O. and director of its medical research, health and accident department, according to the Detroit *News*. In letters to the Michigan State Medical Society and the Wayne County Medical Society, Addes asked that they make investigations and "take immediate steps to stop the many trick devices that are being used to lure money away from the workers through false pretenses."

NEW JERSEY

Dr. Vail Observes Ninety-Eighth Birthday.—Dr. William H. Vail, Newark, the oldest living alumnus of Princeton University, celebrated his ninety-eighth birthday, August 4. Recently the university took title to the house occupied by Dr. Vail so that he could live there "as long as he may desire" (THE JOURNAL, June 19, p. 552). Dr. Vail, who was a member of Princeton's class of 1865, is also said to be the oldest living alumnus of the College of Physicians and Surgeons of Columbia College, New York, where he graduated in 1869.

NEW YORK

Personal.—Dr. Richard Nauen, senior tuberculosis physician of the New York State Hospital, Ray Brook, has been appointed tuberculosis control director of Cattaraugus County and superintendent of the county sanatorium.——Dr. Nicholas J. Colao, Peekskill, was chosen president of the city board of education, July 6, for the ensuing year.

New York City

Venereal Disease Activities.—The bureau of social hygiene of the New York City Department of Health now has facilities for darkfield examinations for syphilis at seventeen social hygiene diagnostic centers. The service is offered without charge to physicians to aid in the diagnosis of early syphilis. New York physicians are eligible for the clinical refresher course in modern methods of diagnosis and treatment of venereal disease conducted during the summer at the city department of health under the direction of Dr. Louis Chargin. The bureau of social hygiene is also making available a number of pamphlets designed to keep the general practitioner up to date on modern methods of the diagnosis and treatment of venereal diseases.

Graduate Courses in Neurology and Psychiatry.—Graduate courses are offered in neurology and psychiatry by Columbia University College of Physicians and Surgeons and cooperating institutes, beginning October 4 and ending December 10. These courses are designed for physicians interested in neurology and psychiatry. In addition to the clinical survey, they aim to cover, in part, the sociological and educational fields. Among these sources of clinical material are the psychiatric and neurologic outpatient departments of the Vanderbilt Clinic, the Psychiatric Institute and Hospital and the Neurological Institute of New York. The courses consist of lectures, laboratory work, demonstrations and practical clinical courses. Any individual course (except clinical assignments in neurology and psychiatry) may be taken singly. Arrangements may be made for an extensive course in neuropathology. The major part of the time is spent in practical laboratory work in the department of neuropathology of the psychiatric institute. Information may be obtained by applying to the Dean of the Faculty of Medicine, Columbia University, 630 West 168th Street, New York 32.

NORTH DAKOTA

Changes in State Health Department.—Dr. Mary E. W. Soules, assistant director of maternal and child hygiene for the North Dakota State Department of Public Health, Bismarck, has been named director, effective August 1, to succeed Dr. Robert G. White, who has been appointed director of the Burke-Minot-Ward district health unit. Dr. George F. Campana, formerly assistant district state health officer in New York, and recently of Albany, N. Y., has been appointed state epidemiologist and director of the division of preventable diseases for North Dakota.

OREGON

State Medical Meeting.—The Oregon State Medical Society will conduct its annual meeting at the University of Oregon Medical School, Portland, September 4-5. The banquet will be in the Benson Hotel, Sunday evening. Many officers from the armed services will participate in the program, which will cover tropical medicine, industrial medicine and military medicine for civilian and combat areas.

SOUTH CAROLINA

Refresher Course.—The Medical College of the State of South Carolina, Charleston, will conduct a refresher course for practicing physicians, November 3-4. The program was inaugurated last year at the request of alumni. Those participating in the course will include Drs. Leroy U. Gardner, Saranac Lake, N. Y.; Alfred Blalock, Baltimore; Roy R. Kracke, Emory University, Ga.; Charles Christian Wolferth, Philadelphia; Virgil P. W. Sydenstricker, Augusta, Ga.; John Theodore King, Colonel, M. C., A. U. S.; Harrison F. Flippin, Philadelphia, and George W. Thorn, Boston.

Dr. Boozer Resigns as Secretary of State Board.—Dr. Albert E. Boozer, Columbia, has resigned as secretary of the South Carolina State Board of Medical Examiners, a position he has held since 1911. He has been a member since 1909. The board recently adopted a resolution acknowledging his able services. Dr. Nathaniel B. Heyward, Columbia, is the new secretary of the board. Dr. Boozer graduated at the University of Pennsylvania School of Medicine, Philadelphia, in 1892. He began private practice in Columbia the same year and was on the first board of physicians of Columbia Hospital. A few years ago he resigned as medical director and examiner for the Carolina Life Insurance Company, a position he held for about twenty years. According to the state medical journal, Dr. Boozer was assistant medical referee with the Mutual Life Insurance Company and the medical referee of the Missouri Life Insurance Company, serving as examiner for twenty-five other life insurance companies.

TEXAS

Community Honors Physician.—Dr. Thomas E. Winford, Dallas, was presented with the W. H. Adamson child welfare trophy for 1943 on July 13. The award, which is given annually to the person in Oak Cliff adjudged to have done the most child welfare work during the previous year, went to Dr. Winford for his work for underprivileged children in the free eye, ear, nose and throat clinic operated at the Dallas Methodist Hospital under the auspices of the Oak Cliff Lions' Club.

Physician Sentenced for Draft Evasion.—Federal Judge T. Whitfield Davidson overruled a motion for a suspended sentence for Dr. Lawrence E. Arnold, Dallas, who is under a two year sentence for draft evasion, newspapers reported. It was

stated that the superintendent of a local hospital and numerous physicians joined in the plea for a suspended sentence because of the service that Dr. Arnold has been performing in treating patients since his sentence and since the departure of so many of the local physicians for the armed services.

WEST VIRGINIA

New Education Plan Begins at West Virginia University.—The fall term of the West Virginia University School of Medicine is scheduled to start September 27 and end December 17. Twenty-five sophomore students, including two women, will complete their work at the end of the term. Of this number twenty will immediately transfer to the Medical College of Virginia, Richmond, under the provisions of the medical education plan recently agreed to by both schools (THE JOURNAL, March 13, p. 877). The other five members of the class have been accepted at the medical schools of the University of Pennsylvania, University of Cincinnati, Temple University and Jefferson Medical College.

WISCONSIN

Found Guilty of Improperly Using Title "Doctor."—Fred Neukom, 63, Winona, Minn., was freed of a charge of practicing medicine without a license in the state of Wisconsin but was found guilty of improperly using the title "doctor" by a municipal court jury in Racine on June 4. According to the *Wisconsin Medical Journal* the charge under which Mr. Neukom was freed was brought as the result of a complaint signed by an investigator for the state board of medical examiners, who had testified that he had been treated by Mr. Neukom on January 27.

Advisory Committee Named to Study Problems of State Institutions.—At the request of the state board of public welfare Dr. Russell M. Kurten, Racine, president of the State Medical Society of Wisconsin, appointed an advisory committee to meet with the board members and study existing problems and policies affecting the state institutions. The new advisory committee, made up of Drs. Horace Kent Tenney Jr. and Henry L. Greene, Madison, Elwood W. Mason and John L. Garvey, Milwaukee, and Wayne A. Munn, Janesville, held its first session on June 24 in Union Grove.

Personal.—Dr. Albert Popp, Milwaukee, has been appointed a police physician and surgeon, succeeding the late Dr. David D. Mehigan.——Dr. Edward P. Evans, Milwaukee, was guest of honor at a luncheon recently marking his retirement as medical examiner of the Equitable Life Assurance Society of the United States after eighteen years in the position.—— Dr. Erwin C. Cary, Reedsville, has been reappointed health officer for the village of Reedsville and also for the towns of Rockland and Franklin. He was recently reelected president of the Manitowoc County Health Officers' Association.

Waukesha Springs Sanitarium Ends Service.—The recent retirement of Dr. Byron M. Caples as head of the Waukesha Springs Sanitarium and the sale of part of the sanatorium property to Carroll College, Waukesha, marks the end of the operation of the institution. The sanatorium was established by Dr. Caples in 1898. He plans to continue his practice in Waukesha and to run a 30 acre farm on the outskirts of the city. The transfer of the property to Carroll College was brought about when the college experienced a housing shortage after cadets of the army air corps had been assigned to the college.

GENERAL

Reprints on Psychosomatic Medicine and Psychiatry Available.—The Josiah Macy Jr. Foundation, New York, has made it possible for the National Committee for Mental Hygiene to distribute a limited number of reproductions or reprints of selected scientific articles bearing on war problems in the field of psychosomatic medicine and psychiatry to medical officers in the armed forces of the United Nations. Medical officers who wish to receive such articles should notify the National Committee for Mental Hygiene, 1790 Broadway, New York 19.

Chinese Medical Journal Resumes Publication.—The *Chinese Medical Journal*, which suspended publication when the Japanese took over the offices of the Chinese Medical Association in Peking in December 1941, is now being issued at P. O. Box 6096, Washington, D. C., as a quarterly, since printing and circulation facilities in Free China are inadequate. However, the medical profession in China still has its Chinese edition. The publication of the journal in the United States has been made possible by the assistance of the Chinese Foundation.

Microfilm and Slide Hand Viewer.—A hand viewer for reading strip films and viewing 2 by 2 slides is now in production and will be on the market within a few weeks. This viewer was designed especially for the use of the medical services of the armed forces through the efforts of the Army Medical Library. Full information with regard to obtaining the viewer, which magnifies approximately ten times and which is definitely in the low price class, will be supplied on request by addressing the Photoduplication Service, Army Medical Library, 7th and Independence Avenue S.W., Washington 25, D. C.

Eye Health and Safety News.—The National Society for the Prevention of Blindness is now publishing a bimonthly newsletter entitled *Eye Health and Safety News* for free distribution among physicians, nurses, public health officials, social workers, educators, safety engineers, and others who are professionally interested in some aspect of sight conservation. Each issue of the *News* contains items on developments and new projects in the campaign for prevention of blindness. A regular feature is the reporting of activities in this field carried on by official voluntary state agencies. Those who are interested in receiving this new publication regularly are invited to write to the society, 1790 Broadway, New York 19.

Conference on Tuberculosis.—The Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Trudeau Society will hold their thirtieth annual meeting at the Edgewater Beach Hotel, Chicago, September 8-9, under the presidencies of Dr. Charles H. Lerrigo, Topeka, Kan., and Dr. Frank L. Jennings, Indianapolis, respectively. In addition to general sessions there will be discussions on health education, war problems, rehabilitation and an x-ray conference. Among the speakers will be:

Dr. George F. Parker, Greencastle, Ind., College Health Services and the War.
Clarence M. Sharp, surgeon, U. S. Public Health Service Reserve, Bethesda, Md., Examination of Industrial Workers.
Dr. Adolph G. Kammer, Chicago, Tuberculosis in Industry.
Dr. Everett K. Geer, St. Paul, Transient Infiltration of the Lung Parenchyma Associated with Eosinophilia.
Lieut. Comdr. Horatio B. Sweetser Jr. (MC), U. S. Naval Reserve, Rheumatic Fever in Young Adults.
Lieut. Col. Esmond R. Long, M. R. C., The Discovery and Disposition of Cases of Tuberculosis in the Army of the United States.

LATIN AMERICA

The Hospital Infantil.—The first children's hospital built by the Mexican government was dedicated in Mexico City on May 29. The second hospital to be completed in the new medical center now under construction, the unit will be used as a teaching hospital for the medical school of the National University and has lecture rooms, class rooms and student laboratories located in the building. Of concrete construction, the building has six floors with a capacity of 550 beds for children of all ages from newborn infants up to 14 years of age. Facilities and services of the hospital include an outpatient clinic with adjoining laboratories for special diagnostic services, inpatient facilities for pediatrics, orthopedic surgery, general surgery, otolaryngology, ophthalmology, neurology and dermatology services, as well as special provisions for physical therapy, occupational therapy and educational and social services. One unit has been specially designed for the care of premature infants. There are also a breast milk station and a well equipped milk laboratory. The department of nutrition, which is responsible for the preparation of food for child patients and employees, is staffed by persons trained in dietetics and is furnished with mechanical refrigerators and other modern equipment. Experienced educational therapy workers will teach invalid or crippled children occupations that they will be able to continue after leaving the hospital, instruct them in their school subjects so that they need not fall behind, and help them in other ways to spend the time in the hospital usefully and pleasantly. Dr. Federico Gómez, Mexico City, is in charge of the hospital and Dr. Juan Farill has been named chief of the orthopedic service.

CORRECTION

Academy of Medicine Receives Endowments.—In a news item the THE JOURNAL, July 31, page 959, announcing the creation of an endowment in perpetuity at the New York Academy of Medicine by R. Thornton Wilson in honor of his wife, the name should have been Frances Ellsworth Wilson and not Frances Elizabeth Wilson.

Foreign Letters

LONDON

(From Our Regular Correspondent)

July 7, 1943.

Science and the State

The necessities of war have led to science playing a more important part in national affairs than ever before. In a letter to the *Times* three leading scientists, R. H. Pickard, chairman of the Joint Council of Industrial Scientists, Alexander Findlay, president of the Royal Institute of Chemistry, and Prof. W. L. Bragg, president of the Institute of Physics, endorse the pleas now being made that scientific effort, so effective in the war, shall not be allowed to cease when peace returns but shall be applied to the problems of reconstruction. They object, however, to the exaggerations of many responsible scientists which often accompany reasonable claims. It is sometimes said that if some fraction of the national income was allocated to scientific research and if scientists were given a position of authority in the state, we would find ourselves in "an age of plenty." Such misleading of the community as to its resources can only foster illusions and bring disappointment. While we may hope that the improvement in our material comforts, which has marked the past fifty years, will be continued, it should be remembered that the fruits of research sometimes ripen slowly and that our material resources during the postwar period cannot be vastly greater than those we now possess.

The claim that the scientist as such is entitled to some position of exceptional authority in deciding the policies of governments is one which cannot be accepted in a democratic community. Social problems are too complex to be solved by any one type of mind. But the scientist can give valuable help in solving problems and could profitably be consulted more frequently. No social problem can be solved solely by the methods of science, for other values are involved than material ones.

Armored Vests for American Airmen

Armored vests to protect the crews of bombers of the United States Eighth Air Force against flak splinters and fragments of explosive shells have been designed and manufactured in England. They have already been worn in several raids and the results are regarded as extremely satisfactory. The vest is made of canvas on which are sewn squares of manganese steel so that they overlap slightly, giving complete protection to the chest and the back. An apron section, suspended from the vest by hooks, is also worn, giving cover as far as the knees. The vest and apron are made in two types, full width for men whose duties cause them to stand and tapered for others. The pilot and co-pilot wear a half vest providing protection only in front, since their backs are protected by armor plate fitted to the aircraft. A full vest weighs 16 pounds, a full apron 6½ pounds.

Col. M. C. Grow, surgeon of the United States Eighth Air Force, is responsible for the development of the idea. After months of operations he found that most of the wounded airmen were injured by low velocity missiles. Whereas armor which would stop everything was not practical, he believed that these low velocity missiles could be stopped by light armor. He went to the headquarters of the London police and was recommended a manufacturer of bullet proof vests. He took a designer from this plant and got him to watch an experienced combat crew in a grounded flying fortress going through the motions of firing the guns and doing their respective jobs. In addition to affording protection, the armor had to meet three specifications: It must not hamper operational efficiency, it must not be so heavy as to produce fatigue and it must be shed quickly in an emergency. The London firm, which has specialized in sword making since 1772, produced an experimental model that met all these specifications. Colonel Grow had the vest tested with a 0.45 caliber army pistol at 30 feet. The bullet did not penetrate even at the joints where the metal plates overlap. Colonel Grow is now working on a close fitting helmet having the same flexibility that the unjoined steel plates give the vest.

Diphtheria as a War Danger

The danger of invasion by diphtheria is mentioned in a report by the Medical Research Council. The history of diphtheria epidemics suggests that our epidemiologic invasion lines run from the south of Europe, and this has to be borne in mind now that North Africa has become a theater of war. Advocating immunization on the widest scale, the report says that, although its value was known almost a generation ago, diphtheria has continued to be a major cause of mortality, and there is reason to think that in certain sections of the population the danger has increased. Though there has been a decline of 60 per cent during the past forty years, it is short of what has been accomplished elsewhere. The mortality is declining more quickly at preschool than at school age. This is explained by the fact that in overcrowded areas the families have become smaller and less crowded owing to improved housing. Hence the children are less exposed to infection in their preschool life but more contract the disease in school life. It has been estimated that 2 to 5 per cent of London school children are carriers of virulent diphtheria organisms. Why they remain healthy in other respects has not been explained, or why some clinical cases always remain in the carrier state.

Postwar Blood Transfusion

The British Red Cross Society announces in its annual report its willingness to organize a national blood transfusion service to come into operation with the end of the war. A much greater demand for blood donors than ever known before in times of peace is expected to arise immediately after the war. The present emergency blood supply depots may cease to function and their places will have to be taken by local services. Conditions as uniform as possible will be necessary, so that donors may be able, when removing to another district, to transfer to the new service with the certainty of finding the same standard of skill, consideration and protection. For this a national organization such as exists in most other countries is necessary. Conferences have been held, at one of which representatives of the fighting services attended, to prepare the basis for this national service.

At the request of the Ministry of Home Security both men's and women's detachments of the Red Cross have been given instruction at military airdromes in the technicalities of giving first aid to crews of crashed aircraft. They have been taught the method of approaching the aircraft, how to get at trapped members of the crew, methods of releasing belts and harnesses, the types of rescue tools carried in the aircraft, where to look for the tools and how to use them, and fire risks. Already lives have been saved by this rescue service.

Mr. R. Watson-Jones Transfers to London

Mr. R. Watson-Jones, orthopedic surgeon, of Liverpool, is to transfer to London. He has accepted the invitation of the London Hospital to join the honorary staff as director of the new Accident and Orthopedic Department. The transfer to London of provincial surgeons has always been a very rare event.

BUENOS AIRES

(From Our Regular Correspondent)

April 16, 1943.

Hypertensive Substance

Drs. L. F. Leloir, J. M. Muñoz, A. C. Taquini, E. Braun Menéndez and C. Fasciolo, all of Buenos Aires, recently reported the results of investigations which were carried on with the aim of ascertaining the origin and mechanism of formation of hypertensive substances. Hypertensinogen is a globulin of the blood plasma which is obtained by a process of fractional precipitation in plasma by means of ammonium sulfate. These investigators do not accept Page and Helmer's theory concerning the presence of hypertensinogen in blood globules. Renin has an effect on hypertensinogen with consequent formation of hypertensin. The seat of origin and mechanism of destruction of hypertensinogen were unknown. Page and his collaborators believe that both the formation and the destruction of the substance occur in the liver and that the mechanism of destruction is similar to that of dextrose. Leloir confirms Page's statement but objects to Page's technic as the latter's studies were made on hepatectomized animals with kidneys, which constitutes a cause of error. Leloir and his collaborators removed several organs which permitted them to identify with certainty the place of formation of the substance. They employed Muñiz's technic for determining the substance in citrated and centrifuged blood. Leloir's method was used for measuring the amount of renin. The authors found that the amount of hypertensinogen does not change in animals with abdominal evisceration. In animals in which hypertensinogen disappeared from the plasma because of an injection of renin the removal of the abdominal viscera with the exception of the liver results in reappearance of hypertensinogen in the plasma in normal quantities. Hypertensinogen is rapidly resynthesized if a plasmogenesis is performed in nephrectomized dogs, but resynthesization does not occur after evisceration. These investigators conclude that hypertensinogen is formed and synthesized in the liver. The substance used by the liver in synthesizing hypertensinogen is not known. When the amount of hypertensinogen in the plasma is highly concentrated, the liver stops production of the substance. Renin changes hypertensinogen into hypertensin, which is eliminated through the kidney.

Congenital Tuberculosis

Dr. Mario Waissmann made observations on 737 tuberculous women who were delivered in the Maternity Department of the Hospital Tornú of Buenos Aires. His observations extended from 1934 to 1942. In the whole group of infants of 737 tuberculous mothers 11 died from congenital tuberculosis (1.46 per cent). Probably the figures would have been higher if necropsy could have been performed systematically. The majority of children from tuberculous mothers grow normally. Congenital tuberculosis develops only when tuberculous lesions are present in the placenta. This occurrence is more frequent in patients with grave forms of tuberculosis than in patients with mild forms of the disease. Transplacental tuberculosis is not necessarily fatal. Dr. Waissmann carried on careful observations on the embryofetal circulation. After the third month of intrauterine life the volume of blood carried to the heart and lungs is considerably increased. That is why pulmonary tuberculosis is the predominant form of congenital tuberculosis. On the basis of the known facts concerning embryofetal circulation, the existence of congenital pulmonary tuberculosis cannot be denied. The differential diagnosis between congenital and acquired tuberculosis in infants is done by ascertaining whether or not the infant was separated from the mother immediately after birth and removed to a safe environment. The only possibility of protecting the infant against tuberculosis is separating it from a tuberculous environment.

Kenny Treatment of Poliomyelitis

An epidemic of poliomyelitis has existed for several months in Buenos Aires. A committee consisting of Dr. Rutherford L. John, associate professor of orthopedic surgery of the University of Pennsylvania School of Medicine, and two nurses recently arrived in Buenos Aires for the purpose of teaching the application of the Kenny method. Various committees of South American physicians, surgeons and orthopedists and three poliomyelitis committees in Argentina organized to carry on the work. Practical sessions for teaching the application of the method were held in the Hospital de Niños and the Muñiz Hospital of Buenos Aires. Dr. John has also given courses on the subject. Large numbers of South American physicians, surgeons and orthopedists were present. Dr. John was especially invited to give lectures to the Argentine societies of pediatrics and orthopedic surgery.

Society Reunion

The first annual meeting of the Society of Rheumatology of Río de la Plata was held in Montevideo, Dec. 18 and 19, 1942, under the auspices of the Liga Uruguaya contra el Reumatism. There was a large attendance of Argentine, Brazilian, Paraguayan and Uruguayan physicians. Resolutions were adopted (1) to consider rheumatic diseases a problem of public health for the government, (2) to ask the government for the organization and establishment of proper centers and hospitals for the prevention and therapy of heart disease and also for hospitalization of convalescents and (3) to give unanimous support to the organization and establishment of the Pan American League Against Rheumatism. A South American committee, the members of which are in charge of preparing a well coordinated terminology of rheumatic diseases, was appointed. It was made up of Drs. Rafael Bullrich, Pedro Cossio and Anibal Ruiz Moreno of Argentina, Genival Soares Londres of Brazil and Fernando Herrera Ramos and Bolivar Delgado Correa of Uruguay. The second annual meeting of the Society of Rheumatology of Río de la Plata will be held in July 1944.

Inexpandable Lung

Drs. Mariano R. Castex and Egidio S. Mazzei of the First Medical Clinic of the Faculty of Medicine of Buenos Aires confirmed by clinical observations the fact that artificial collapse therapy of pulmonary tuberculosis may be the cause of inexpansibility of the lung with consequent chronic pneumothorax, pleurisy and some other diseases. Inexpansibility may also follow pleurolysis and operation for empyema. In cases of inexpansibility of the lung of intrinsic origin, respiration in mechanical chambers may produce an acceptable degree of reexpansion and prevent the need of a thoracoplasty. In cases of retention of secretions in the bronchi the therapy by the bronchial route is useful and may make operation unnecessary.

Brief Items

The government of Argentina made an allowance of 5,981,960 Argentine pesos for the 1943 budget of some university clinics and of some other scientific institutions. The budget of the Faculty of Medicine of Buenos Aires is for 3,713,340 pesos. That of a group of other scientific institutions is for a total amount of 2,268,620 pesos.

Dr. Nicolás Romano of Buenos Aires was recently appointed to the chair of clinical medicine of the Faculty of Medicine of Buenos Aires, which was made vacant through the resignation of Dr. Rafael Bullrich. Dr. Romano has been professor of the second chair of clinical medicine of the Faculty of Medicine of the University of La Plata since 1935. He is the president of the Argentine Medical Association and the author of various important books on clinical medicine, respiratory diseases and other subjects.

Deaths

Lonnie Bondurant Moseley, Jackson, Miss.; University of Virginia Department of Medicine, Charlottesville, 1927; fellow of the American College of Surgeons; member of the Mississippi State Medical Association; commissioned a lieutenant in the medical corps of the U. S. Naval Reserve in November 1940 and later promoted to lieutenant commander; was discharged, Dec. 17, 1942, on account of physical disability; served for a time in the Solomon Islands and the Far Eastern area; served as attending urologist to the Jackson Infirmary and visiting urologist to the Mississippi State Charity Hospital, Jackson, Mississippi State Hospital, Whitfield, and the Mississippi State Tuberculosis Sanatorium, Sanatorium; aged 40; died, July 6, of heart disease.

Raymond Force Longacre ● Major, U. S. Army, retired, West Los Angeles; Medico-Chirurgical College of Philadelphia, 1891; served during World War I; commissioned a major in the medical corps of the U. S. Army in 1920 and retired in 1931 for disability in line of duty; in 1932 was appointed medical director of the Aeronautics Branch, U. S. Department of Commerce; in 1924 went to the Philippines to become surgeon at Nicols Field, Manila; in 1927 became post surgeon at Bolling Field, Wash., and in April 1928 was appointed assistant chief of the medical division of the army air corps; aged 75; died, February 19, of cerebral hemorrhage and arteriosclerosis.

Francis Marion McCallum, Kansas City, Mo.; Ensworth Medical College, St. Joseph, 1893; member of the House of Delegates of the American Medical Association in 1915 and 1926; member of the American Urological Association; fellow of the American College of Surgeons; veteran of the Spanish-American War; served as a captain and assistant surgeon in the medical corps of the U. S. Army for many years; past president of the state board of health; in 1934 appointed first commissioner of social disease control for the city health department; chief of the urologic service of the Kansas City General Hospital from 1911 to 1934; aged 76; died, June 26.

William Humphrey Mackinney ● Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1903; professor of urology and vice dean for urology at the Medico-Chirurgical College, Graduate School of Medicine, University of Pennsylvania; member of the American Urological Association and the Philadelphia Genito-Urinary Society; specialist certified by the American Board of Urology, Inc.; aged 62; on the staffs of the Mary Drexel Home, Philadelphia General Hospital, Children's Hospital, Graduate Hospital of the University of Pennsylvania and the Lankenau Hospital, where he died, June 9, of arteriosclerotic heart disease.

James Ritchison Breakey, Ypsilanti, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1889; member of the Michigan State Medical Society; on the staff of the Beyer Memorial Hospital; aged 79; died, June 22, in the University Hospital, Ann Arbor, of bronchopneumonia.

Alonzo Alcesta Browning, Phoenix, Ariz.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1908; member of the Arizona State Medical Association; on the staff of the Good Samaritan Hospital; aged 58; died, June 24, of a malignant tumor of the chest.

Minnette Burnham, Honolulu, Hawaii; Woman's Medical College of Pennsylvania, Philadelphia, 1899; for many years a medical missionary; aged 75; served on the staff of the Queen's Hospital, where she died, April 4, of cerebral hemorrhage.

John Henry Busch, Binghamton, N. Y.; College of Physicians and Surgeons, Baltimore, 1885; aged 81; died, May 29, of carcinoma of the stomach.

Elizabeth D. Carroll, Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1910; senior attending physician to the Chicago State Hospital; aged 62; died, June 26, of carcinoma.

Joshua Anderson Chafin, Griffithsville, W. Va.; University of Louisville (Ky.) Medical Department, 1907; aged 57; died, June 22, in the Pinecrest Sanitarium, Beckley, of tuberculosis.

Alice Maud Mary Chesley-Lamprey, Exeter, N. H.; Tufts College Medical School, Boston, 1900; member of the New Hampshire Medical Society; past president of the Rockingham County Medical Society; on the advisory staff of the New Hampshire Memorial Hospital, Concord; served as examining physician at the Robinson Seminary, Exeter, University of New Hampshire, Durham, and the Bradford (Mass.) Junior College; aged 81; on the staff of the Exeter Hospital, where she died, June 30.

Melville L. Combes, Cleveland Heights, Ohio; Cleveland Medical College, 1895; formerly on the staff of the Huron Road Hospital, Cleveland; aged 76; died in St. Petersburg, Fla., June 28, of hypostatic pulmonary congestion.

Samuel Austin Daniel, Welch, W. Va.; Kentucky School of Medicine, Louisville, 1894; member of the West Virginia State Medical Association; served as sheriff of McDowell County from 1916 to 1920 and as mayor of Welch; aged 74; died, July 20, of heart disease.

Orr Abraham Dickson ● Jefferson, Ohio; Starling Medical College, Columbus, 1898; served as a captain in the medical corps of the U. S. Army during World War I; member of the staff of the Ashtabula (Ohio) General Hospital; aged 70; died, June 29, in St. Vincent's Hospital, Erie, Pa., of chronic nephritis and uremia.

Charles Reed Garraway, Mobile, Ala.; Hospital College of Medicine, Louisville, Ky., 1907; aged 58; died, June 7, in Laurel, Miss., of injuries received in an automobile accident.

Charles V. Genoway ● Boise, Idaho; Medical College of Ohio, Cincinnati, 1888; member of the Radiological Society of North America, Inc.; at one time health officer of Spokane, Wash.; on the staff of St. Alphonsus Hospital; aged 79; died, June 18, of coronary thrombosis.

Robert Winston Giles, Corpus Christi, Texas; University of Tennessee College of Medicine, Memphis, 1939; entered the medical reserve corps of the U. S. Army, Dec. 29, 1940, and resigned as a first lieutenant, July 10, 1941; aged 37; died, May 16, in the Gartly-Ramsay Hospital, Memphis, of gastric ulcer and pneumonia.

James Edward Ginter, Du Bois, Pa.; Medico-Chirurgical College of Philadelphia, 1908; member of the Medical Society of the State of Pennsylvania and the Radiological Society of North America, Inc.; on the staff of the Du Bois Hospital; aged 62; died suddenly, June 28, of coronary thrombosis.

Irving Waterloo Greene ● Owosso, Mich.; University of Michigan Medical School, Ann Arbor, 1913; instructor in internal medicine at his alma mater from 1922 to 1924; fellow of the American College of Physicians; secretary of the Shiawassee County Medical Society; served in the medical corps of the U. S. Army during World War I; on the staff of the Memorial Hospital; aged 53; died, June 28, of coronary thrombosis.

James Dixon Hall, Sanatorium, Texas; University of Texas School of Medicine, Galveston, 1939; a member of the staff of the State Tuberculosis Sanatorium; aged 26; died, June 24.

James Field Hall, Oklahoma City; Louisville (Ky.) Medical College, 1896; aged 70; died, June 17, of heart disease.

Olaf O. Haraldson ● Minot, N. D.; Rush Medical College, Chicago, 1912; health officer of Ward County and Minot; member of the staffs of the Trinity and St. Joseph's hospitals; aged 58; died, June 6, in Northwood of cerebral hemorrhage.

Leslie A. Howe, Breckenridge, Mich.; University of Michigan Homeopathic Medical School, Ann Arbor, 1890; member of the Michigan State Medical Society; served as a member of the school board, village president and village clerk and on the staff of the R. B. Smith Memorial Hospital, Alma; aged 76; died, June 25, of coronary occlusion.

Richard S. Hughes, Ocala, Fla.; Meharry Medical College, Nashville, Tenn., 1905; aged 61; died, June 12, of cerebral hemorrhage.

Gerald Charles Hunt, Springfield, Ill.; University of Illinois College of Medicine, Chicago, 1916; member of the Illinois State Medical Society and the American Urological Association; served overseas during World War I; member of the staffs of the Memorial and St. John's hospitals; aged 52; died, May 15, of coronary occlusion.

William Jefferson Hutson, Eudora, Ark.; Memphis (Tenn.) Hospital Medical College, 1909; member of the Arkansas Medical Society; aged 60; on the staff of the Lake Village (Ark.) Infirmary, where he died, June 20, of heart disease.

Leroy Anthony Jackson, Shreveport, La.; Meharry Medical College, Nashville, Tenn., 1927; aged 47; died, June 23.

Samuel A. Jahss ● New York; Long Island College Hospital, Brooklyn, 1913; specialist certified by the American Board of Orthopaedic Surgery, Inc.; member of the Ameri-

can Academy of Orthopedic Surgeons; attending orthopedic surgeon to the Hospital for Joint Diseases and the Sydenham Hospital; aged 51; died, May 31, of coronary thrombosis.

John H. Jarvin, Chicago; Chicago Medical School, 1920; also a dentist; aged 56; died, June 21, of coronary thrombosis.

Charles Albert Johnson, Bruce, Miss.; Memphis (Tenn.) Hospital Medical College, 1894; aged 82; died, June 30, of angina pectoris.

Wiley Carroll Johnson ● Canton, N. C.; Medical Department of Tulane University of Louisiana, New Orleans, 1912; member of the school board of Canton; member of the examining staff of the Selective Service System; aged 56; on the staff of the Norburn Hospital, Asheville, where he died, June 10, of acute nephritis.

Ernest Kaltenbach, St. Joseph, Mo.; St. Joseph Hospital Medical College, 1882; aged 87; died, June 13, of a ruptured gallbladder.

John Francis Kane ● Olean, N. Y.; University of Buffalo School of Medicine, 1901; aged 65; member of the staffs of St. Francis Hospital and the Olean General Hospital, where he died, June 16, of acute cardiac dilatation.

Morris Kassel ● Brooklyn; Columbia University College of Physicians and Surgeons, New York, 1919; aged 48; died, June 10, of acute coronary thrombosis.

Gilbert Giles Kesner, Burlington, Kan.; University Medical College of Kansas City, Mo., 1903; aged 61; died, May 30, in the Newman Memorial County Hospital, Emporia, of gastric ulcer.

John H. F. Krueger, Des Plaines, Ill.; National Medical University, Chicago, 1909; Bennett Medical College, Chicago, 1912; served on the staff of the Walther Memorial Hospital, Chicago; aged 62; died, July 3, of myocarditis.

Leo Lieberman, New York; University and Bellevue Hospital Medical College, New York, 1909; aged 68; died, May 24, of heart disease.

Frederick King Lord, Ceres, Calif.; Louisville (Ky.) Medical College, 1894; served during World War I; a first lieutenant in the medical reserve corps of the U. S. Army not on active duty; aged 75; died, June 28, in a hospital at Modesto.

Clark McEwen Luman ● Uniontown, Pa.; Jefferson Medical College of Philadelphia, 1904; fellow of the American College of Surgeons; on the staff of the Uniontown Hospital; aged 65; died, June 29, in Hopwood.

Cynthia Estella Pingree Macnider, Jamestown, N. D.; College of Physicians and Surgeons, Boston, 1890; aged 84; died, May 4, in the Jamestown Hospital of chronic myocarditis and chronic nephritis.

James William Magruder, Mechanicsburg, Ohio; Miami Medical College, Cincinnati, 1896; aged 72; died, April 16, of heart disease.

Ferdinand Maddin Malone, Capleville, Tenn.; Memphis (Tenn.) Hospital Medical College, 1903; member of the Tennessee State Medical Association; aged 85; died, June 25, in the Methodist Hospital, Memphis, of pneumonia.

Marcus Markiewicz, New York; Long Island College Hospital, Brooklyn, 1885; member of the Medical Society of the State of New York; aged 85; died, June 15, of kidney infection, pneumonia and aneurysm of the aorta.

Jessie Marsh, Chicago; Chicago College of Medicine and Surgery, 1914; member of the Illinois State Medical Society; aged 59; died, June 30, in St. Bernard's Hospital of cerebral hemorrhage.

Albert Henry Marshall ● Topeka, Kan.; University of Oklahoma School of Medicine, Oklahoma City, 1914; also a pharmacist; member of the executive committee and past president of the staff of the Stormont Hospital; medical director of the American Home Life Insurance Company; for many years surgeon for the Rock Island Railroad; aged 67; died, June 7, of coronary occlusion.

Nicholas Joseph McCaul ● Brooklyn; Baltimore Medical College, 1906; member of the staffs of the Shore Road and Samaritan hospitals; served during World War I; aged 63; died, June 19, of coronary sclerosis.

Andrew M. McGovern ● Lawton, Pa.; Baltimore Medical College, 1903; aged 66; died, June 14, of heart disease.

George McGuffin, Pettisville, Ohio; Western University Faculty of Medicine, London, Ont., Canada, 1900; member of the Ohio State Medical Association; secretary-treasurer of the Fulton County Medical Society; clerk of the school board; aged 71; member of the staff of the De Ette Harrison Detwiler Memorial Hospital, Wauseon, where he died, May 10, of arteriosclerosis.

Edmond Mortimer Prince, Birmingham, Ala.; Medical College of Alabama, Mobile, 1901; member of the Medical Association of the State of Alabama; served as a captain in the medical corps of the U. S. Army during World War I; fellow of the American College of Surgeons; aged 67; died, June 4.

Walton Higby Rea, Topeka, Kan.; Barnes Medical College, St. Louis, 1905; member of the Kansas Medical Society; formerly on the staffs of the Mercy Hospital, Arkansas City and St. Mary's and the William Newton Memorial hospitals, Winfield; aged 64; died in Christ's Hospital, May 26, of cerebral hemorrhage.

John Rudolph Rose, Sale City, Ga.; American Medical College, St. Louis, 1877; Atlanta Medical College, 1896; member of the Medical Association of Georgia; aged 86; died, May 13, in the University Hospital, Augusta, of senility.

John Kestley Rupert, Alamosa, Colo.; University of Buffalo School of Medicine, 1896; member of the Colorado State Medical Society; aged 68; president of the staff of the Community Hospital, where he died, May 22, of uremia.

Walter Byron Scott, Ray, N. D.; Queen's University Faculty of Medicine, Kingston, Ont., Canada, 1897; also a pharmacist; at one time mayor of Ray; aged 69; died, May 12, of coronary occlusion.

Charles Augustus Stimson ● Eaton Rapids, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1891; member of the American Proctologic Society; aged 76; part owner of the Stimson Hospital, where he died, May 25.

David Clemington Studebaker, Slippery Rock, Pa.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1915; served during World War I; aged 65; died, April 12, in the Jameson Memorial Hospital, New Castle, of pulmonary embolism.

Eugene Michael Sullivan, Jersey City, N. J.; University of Maryland School of Medicine, Baltimore, 1906; aged 64; died, May 2, of injuries received in a fall.

Leslie Chapman Tilden, Oberlin, Kan.; University of the City of New York Medical Department, New York, 1889; member of the Kansas Medical Society; aged 76; died, May 17, of carcinoma of the liver, stomach and pancreas.

DIED WHILE IN MILITARY SERVICE

Charles Alonzo Anderson, Hinton, W. Va.; University of Virginia Department of Medicine, Charlottesville, 1939; began active duty as a first lieutenant in the medical reserve corps of the U. S. Army in March 1941 and was later promoted to captain; aged 28; was killed, March 7, in an airplane accident at New Orleans.

Frank Cone, Houston, Texas; Johns Hopkins University School of Medicine, Baltimore, 1938; member of the State Medical Association of Texas; appointed a first lieutenant in the medical reserve corps of the U. S. Army in September 1940; later promoted to captain; aged 32; died in the Philippines, June 11, of carcinoma of the ascending colon while a prisoner of war of the Japanese.

Alvin Joseph Leon ● Mystic, Conn.; Tufts College Medical School, Boston, 1928; diplomate of the National Board of Medical Examiners; began active duty as a captain in the medical corps, Army of the United States, in July 1942; aged 40; died, June 21, of arteriosclerosis.

Jack Irvin Smith, Mooresville, Ala.; Vanderbilt University School of Medicine, Nashville, Tenn., 1938; appointed a first lieutenant in the medical reserve corps of the U. S. Army, Jan. 1, 1941, and was later commissioned a captain; aged 28; was killed in an airplane accident, Oct. 1, 1942.

Volt Hung Tom, Honolulu, Hawaii; University of Minnesota Medical School, Minneapolis, 1941; diplomate of the National Board of Medical Examiners; began active duty as first lieutenant in the medical corps, Army of the United States, in March 1942; aged 27; died, March 29, of cerebral malaria.

Bureau of Investigation

STIPULATIONS

Agreements Between Federal Trade Commission and Promoters of Various Products

The following items are abstracts of stipulations in which promoters of "patent medicines," medical devices and cosmetics have cooperated with the Federal Trade Commission to the extent of agreeing to discontinue certain misrepresentations in their advertising. These stipulations differ from the "Cease and Desist Orders" of the Commission in that such orders definitely direct the discontinuance of misrepresentations. The abstracts that follow are presented primarily to illustrate the effects of the provisions of the Wheeler-Lea Amendment to the Federal Trade Commission Act on the promotion of such products.

Amor Skin.—That this product or any other preparation of substantially the same composition, whether sold under the same or a different name, will feed or nourish the skin or that its use will improve the structure or tissue of the skin or have any effect on the contour of the elbow, were misrepresentations which the Amorskin Corporation of New York agreed to drop from their advertising in a stipulation that they signed in January 1943 with the Federal Trade Commission.

Beecham's Laxative Pills.—Beechams Pills, Inc., Bloomfield, N. J., and Atherton and Currier, Inc., New York advertising agency, stipulated with the Federal Trade Commission in October 1942 that they would discontinue any advertisement which failed to reveal that these pills should not be used when abdominal pain, nausea, stomach sickness or other symptoms of appendicitis are present; provided, however, that such advertisements need only contain the statement, "Caution: Use only as directed," if the directions for use, wherever they appear on the label or in the labeling, contain a warning to the same effect.

Breosan Products.—These are put out by a Paul Sturzenegger, trading as Breosan Laboratories, Long Island City, N. Y. In January 1943 Sturzenegger entered into a stipulation with the Federal Trade Commission in which he agreed to discontinue the following representations in his advertising: that the "Breosan Treatment" or "Breosan Suppositories" have any value in the treatment of hemorrhoids other than as an emollient and palliative; that "Breosan Solution" is prophylactic or antiseptic, will cause wounds to heal without scars or promote the growth of new tissue, is not a drug or has any beneficial effect in the treatment of wounds, abrasions, blood poisoning, boils or other ailments enumerated in his advertisements, or that either "Breosan Ointment" or "Breosan Lanolin" has any beneficial effect in the treatment of wounds of many kinds, burns, chapped hands or similar disorders.

Coates Tablets.—These are alleged food preparations comprising "C8 Vegetable Tablets," "B5 Vegetable and Dulse Tablets," "B6 Tablets," "B3 Vegetable Tablets," "BA Vegetable Tablets," "C16 Vegetable Tablets" and "C11 Tablets." They are put out by a Bertha B. Johnson, trading as Coates Concentrates, Chicago. In January 1943 the Federal Trade Commission announced that it had accepted a stipulation from her in which she agreed to cease representing that these products will correct, prevent or overcome mineral or vitamin deficiencies, provide more minerals and vitamins than one would obtain from assimilating two pounds of fresh vegetables; that her nostrums will provide an alkaline balance or are tissue building or rich in vitamins or minerals; that they will provide a substantial amount of silicon for the enamel of bones and teeth; that they will preserve youthfulness, relieve pain, balance weight, or heal; that they are a brain or nerve food or are important to the liver, kidneys, spleen or pancreas or provide laxative effects; that the C11 Tablets will relieve symptoms of high blood pressure or that the B6 Tablets are a tonic or will overcome "tired feeling." Bertha B. Johnson further agreed to discontinue any advertising which failed to reveal that her "C14 Tablets" and "Coates Concentrates C12 Laxative Tonic Tablets" should not be used when stomachache, nausea, vomiting or other symptoms of appendicitis are present; provided, however, that such advertisement need only contain the statement, "Caution: Use only as directed," if and when the directions for use in the labeling contain a warning to the same effect. The respondent further stipulated that she would discontinue representing that neither of these preparations contains drugs.

"Dr. Coleman" Mattresses.—These and some studio couches bearing the same brand name, have been put out by the Gerson Bedding Company, Lowell, Mass. This concern, in January 1943, stipulated with the Federal Trade Commission that it would cease using the word "doctor" or the abbreviation "Dr." either alone or in connection with the name for any of its products so as to convey the impression that they have been made in accordance with the design of, or under the supervision of, a medical practitioner or that such products contain special scientific or health measures which are the result of medical determination or the services of a doctor of medicine; provided, however, that if the name "Dr. Coleman" is used in connection with the marking, branding, or labeling of mattresses made in accordance with the directions of, or under the supervision of, the named person, it shall be immediately accompanied by some other word or words such as "Osteopath," "Osteopathic Physician" or "Doctor of Osteopathy" so as to indicate clearly that the named person is other than a medical practitioner. The concern further agreed to cease using the word "health" either alone or in connection with any other words, as descriptive of mattresses, so as to convey the belief that the products have therapeutic qualities which would be of value in connection with the cure or prevention of diseases or that they are of such nature as would guarantee or assure health to or the maintenance of health by their users.

Halex.—In January 1943 one A. P. Klase, trading as Halex Company, Sappington, Mo., stipulated with the Federal Trade Commission that he would discontinue representing, among other things, that this product is of value for hay fever, asthma, catarrh, migraine, sinusitis, toothache, cold sores, drowsiness, fainting spells, lung colds, influenza or sore throat.

La Vida Mineral Water and La Vida Blue Label Water.—These are put out by La Vida Bottling Company, Inc., Placentia, Calif. In January 1943 Paul G. Hausman, president, William N. Miller, vice president, and Alfred D. Mitchell, secretary, of this concern signed a stipulation with the Federal Trade Commission, agreeing to discontinue the following misrepresentations in their advertising: that the products named have any therapeutic effect other than that afforded by their sodium bicarbonate content or that they are competent remedies or effective treatments for kidney and gallstones, diabetes, neuritis, rheumatism, stomach ailments, liver and bladder troubles caused by excess acid, or the condition resulting from excessive indulgence in alcohol; or that the products attack any ailment at its very foundation or add any minerals to the system in adequate quanity. They also agreed to stop representing that the usual or ordinary diet is "highly acid-forming"; that cooking destroys the alkaline content of foods, or that the respondents' products can be depended on to restore alkaline balance.

Sorature.—Under this brand name are sold certain surgical supplies, including wound clips, by a Belle Propper and a Seymour Schumann, trading as Dr. Propper Manufacturing Company, New York. According to a release issued by the Federal Trade Commission in February 1943, these two persons signed a stipulation with the Commission in which they agreed to discontinue the word "Manufacturing" or the abbreviation "Mfg." or any other word or term of like meaning as part of their trade name. Further, they agreed not to use such word or term in any manner implying that they actually own, operate or directly control the factory in which the products which they sell are manufactured. The stipulation further provided that these persons would no longer use the abbreviation "Dr." or any other word or term of like meaning as part of their trade name, and that they would cease using such abbreviation in a manner which might tend to convey the belief that the wound clips were designed by or manufactured under the supervision of a physician.

Shampo-Kolor.—This was described by the Federal Trade Commission as a coal-tar hair dye sold by Valligny Products, Inc., New York. In December 1942 the Commission reported that it had accepted a stipulation from the Valligny concern in which the latter agreed to cease disseminating any advertisements which did not conspicuously carry the warning: "Caution: This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness." The stipulation provided, however, that such advertisement need contain only the statement, "Caution: Use only as directed on the label," if such label bears the first described caution conspicuously and the accompanying labeling bears adequate directions for such preliminary testing before each application. Incidentally, in April 1940 the Commission had definitely ordered the Valligny concern to discontinue certain representations in the sale of "Shampo-Kolor." Among these were that the product is capable of coloring the roots of the hair or affecting the color of new growth hair; that the use of this product restores the color to the hair, that it is made in France and is "uniquely different or entirely revolutionary in methods or results."

Vitamalt and Natura Calcium Compound and Vitamost.—These are sold by one Frank E. Carter, trading as Three Palms Pharmacy, Los Angeles. In January 1943 the Federal Trade Commission reported that this person had signed a stipulation with the Commission in which he agreed to desist from representing that either of these preparations has any reducing action, or that any weight loss resulting from following the directions for their use is other than such as would naturally result from a starvation diet or abstinence from food; that these nostrums or the diet prescribed therewith can be depended on to bring about weight reduction of ten pounds in five days or that such diet will effectuate any weight reduction in excess of that resulting therefrom; that the diet prescribed with "Vitamalt" will not cause or result in weakness or hunger; that the use of either product with rich food has any building tendency or any practical significance from the standpoint of caloric intake; that either will give new life or freshness to the skin or free it from pimples or blotches, keep the glands and nerves functioning or nourished, have any beneficial effect on the body metabolism, "vitalize" the system, cause the pains of rheumatism, arthritis or lumbago to disappear or provide a competent treatment for nervousness, rheumatism, stomach trouble or constipation. Carter further agreed to cease representing that taking either product as directed will cause a weight reduction safely without lowering resistance to disease or otherwise endangering the health; that Vitamalt is a tonic or that the "Vitamalt Way" of allegedly reducing weight does not consist of fasting; that Vitamalt supplies all the needed vitamins or that the specific function of vitamins is to feed the various glands of the body; that the administration of vitamins in excess of ordinary requirements will result in health, superior physical condition or strength, or increase resistance.

Correspondence

TUBEROUS SCLEROSIS AND TOXOPLASMIC ENCEPHALOMYELITIS

To the Editor:—I agree with the opinion expressed by Drs. Merritt and Aring in their communication to THE JOURNAL, July 24, page 892, with regard to the diagnosis on the father and son described under the heading of "Familial Tuberous Sclerosis (Epiloia) Without Adenoma Sebaccum" in the issue of June 12. The authors apparently have not only misinterpreted the significance of the ocular findings in case 1 but did not recognize the negative diagnostic importance of their absence in case 2.

The presence of ocular lesions with special reference to retinal and to chorioretinal morbid processes in tuberous sclerosis and in toxoplasmic encephalomyelitis (particularly the infantile, or congenital, form of the latter), respectively, in essentially all cases is high on the list of the established criteria for the clinical diagnosis of these disease entities (Koch, F. L. P., and Walsh, M. N.: Syndrome of Tuberous Sclerosis, *Arch. Ophth.* **21**: 465 [March] 1939. Koch, F. L. P.; Wolf, Abner; Cowen, David, and Paige, Beryl H.: Toxoplasmic Encephalomyelitis, *ibid.* **29**: 1 [Jan.] 1943).

Typical retinal tumors not unlike the surface of an unripe mulberry in appearance invariably occur in tuberous sclerosis, while in congenital or infantile toxoplasmic encephalomyelitis there are seen essentially without exception bilateral, more or less atrophic as well as pigmented, central (or macular) as well as more peripheral, fairly extensive patches of chorioretinitis. It is most probable that the onset of these patches in their acute phases occurs prenatally or in infancy or in both but not in childhood or later. There is no reason, however, to suppose that they do not continue to exist throughout the life of the afflicted patient or that they do not remain diagnostically recognizable. The latter is equally true with regard to the characteristic tumors of the optic disk and of the retina in tuberous sclerosis, an entity in which chorioretinitis has not yet been observed as such probably for the very good reason that the tumors are not inflammatory or micro-organistic in origin.

It had been thought that these tumors manifested themselves primarily as proliferations of embryonal cell rests during the complex changes attendant on puberty and adolescence until Givner reported his case (Tuberous Sclerosis, *ibid.* **27**:1234 [June] 1942). In the discussion following the presentation of that case I raised the question of differential diagnosis with respect to toxoplasmic encephalomyelitis, which at that time was under intensive investigation in the Columbia-Presbyterian Medical Center especially with regard to the diagnostic significance of the ocular lesions. It became obvious during the study not only that it was necessary to conduct entirely objective examinations of the eyes and of the eyegrounds but also that it was imperative to avoid the diagnostic pitfalls inherent in the tendency to relegate certain apparently associated diseases to a single clinical wastebasket merely to serve the false purposes of categorical simplification.

I refer particularly to the so-called phakomatoses of van der Hoeve (Eye Symptoms in Phakomatoses, *Tr. Ophth. Soc. U. K.* **52**:380, 1932)—the "related" neurocutaneous syndromes of tuberous sclerosis (diffuse neurospongioblastosis), von Recklinghausen's neurofibromatosis, von Hippel-Lindau's retinal and cerebral angiomatosis and Sturge-Weber's angiomatosis cerebri—none of which have a common clinicopathologic background except for the hypothesis that their occurrence might possibly support Cohnheim's embryonal cell rest theory. There is no valid reason for the clinical misrecognition of any one of these syndromes, nor should there be interconfusion with toxoplasmic encephalomyelitis. The presence of the ocular lesions, or their absence, is pathognomonic in the main and, together with their correlation with the already full reported confirmatory findings inclusive of the usually informative history, should lead to accurate diagnoses in all instances.

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"PSYCHOANALYSIS AND THE SCIENTIFIC METHOD"

To the Editor:—Will you permit me to comment on the important editorial "Psychoanalysis and the Scientific Method" (THE JOURNAL, July 17). Taken as a whole, the article is correct. The obscure sentence that you quote from the psychoanalytic article is not only significant but typical. Any physician who will go to a medical library and read through four or five issues of psychoanalytic journals will find the same type of sentence—or even worse ones—over and over again. The conclusion is inescapable that to this involved and obscure language there must correspond an involved and obscure type of thinking. But it must be pointed out that this criticism does not apply to Freud himself. In expression, in thinking and in style he was always clear, and his greatest contribution is that he drew human problems into the range of scientific inquiry and gave tremendous impetus to the humanizing of psychiatry. It is a strange paradox of medical history that so many of his present day followers have become so unclear and needlessly esoteric.

The Association for the Advancement of Psychotherapy is making a serious attempt to develop Freud's ideas and methods along lines that appear to us more clinically practical and more scientific. One of our aims is to abbreviate the long procedure of psychoanalysis and to bring it into closer relationship with other branches of medicine and psychotherapy.

Constructive abbreviation of the long and expensive psychoanalytic procedures does not consist merely in shortening them; they must be changed as well. Such abbreviation is of great importance for many patients who otherwise cannot get the benefits of psychoanalysis at all, and it also remedies to a large extent the two difficulties mentioned in your editorial, namely the treatment of members of the medical profession and the question of the training of psychoanalysts.

May I draw your attention to some books—Frink's Morbid Fears and Compulsions, Gutheil's Language of the Dream and Wertham's Dark Legend—which demonstrate that the most complex problems and facts of psychoanalysis can be simply and clearly expressed, so that any physician can understand and use them.

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Director, Mental Hygiene Clinic, Queens General Hospital.

PREVENTION OF DYSENTERY BY THE USE OF SULFAGUANIDINE

To the Editor:—The account by Scott of the successful prophylactic use of sulfaguanidine against bacillary dysentery interested me because of a somewhat similar personal group experience.

On an earlier visit to Mexico all in our party suffered the discomfort of what appeared to be a very prevalent tourist affliction—dysentery. On a second visit in March 1942 the three of us took a prophylactic bedtime dose of only 0.5 Gm. of sulfaguanidine. (At this hour the drug would have the least dilution with bowel content and have the longest stay in the intestinal tract.) Despite what seemed a 90 per cent incidence of dysentery (some, severe cases) in our fellow travelers, none of us had the slightest gastrointestinal symptoms.

S. H. IMBODEN, M.D., Reading, Pa.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Workmen's Compensation Acts: Suicide While Mentally Depressed Because of Effects of Industrial Injuries.—During the course of his employment Barber fell astride a hopper, rupturing his urethra and injuring his bladder. Pain in the back and pelvic region, frequency of urination and sexual impotence developed. He became moody and despondent and about a year after the industrial accident committed suicide by slashing his wrists. His widow sought compensation under the workmen's compensation act of Wisconsin, alleging that the pain and loss of sexual powers resulting from the industrial accident produced a mental depression and caused the workman to commit suicide. The industrial commission of Wisconsin found that because of his physical condition, which was due to the industrial accident, the workman developed a psychosis, causing him to become devoid of normal judgment; that in all probability he would not have committed suicide had it not been for the results of the industrial accident but that he had rational knowledge of the consequences of his act and acted with conscious volition to produce his own death; that the suicide did not result from insanity of such violence as to cause him to produce death in a delirium or frenzy, nor while suffering severe pain; and that the workman's act in committing suicide was an intervening cause for death and that therefore suicide and death did not proximately result because of the industrial injury. Compensation was accordingly denied the widow. The circuit court, Dane county, in effect, affirmed the action of the commission and the widow appealed to the Supreme Court of Wisconsin.

The findings of the industrial commission, said the Supreme Court, indicate that the industrial injury to Barber produced certain physical disabilities, that the pain and humiliation involved in these disabilities created for him what was an intolerable condition, and that he became profoundly depressed. With full knowledge of what he was doing he chose deliberately to end his life as an escape from these intolerable conditions. His morbid mental condition had not, however, progressed to the state of insane frenzy. He still had moderately intelligent mental power, rational knowledge of the consequences of his act, and the capacity for conscious volition. On these facts, the commission and the trial court correctly denied compensation to the widow for two reasons. First, section 102.03(1), Stats. (a section of the workmen's compensation act), excludes compensation for intentionally self-inflicted injuries. It is evident that death by suicide constitutes an intentionally self-inflicted injury, and where the insanity of the person so ending his life has not progressed to the stage of destroying capacity to entertain an intention, the statute plainly excludes compensation for the injury. Findings by the commission to the effect that Barber did not act on uncontrollable impulse or in a delirium of frenzy, but with conscious volition and in the exercise of a moderately intelligent mental power, with knowledge of the purpose and effect of his act, seem quite clearly to preclude recovery because of the exclusion of the section under discussion. Secondly, compensation must be denied the widow because the voluntary, wilful act of suicide resulting from a moderately intelligent power of choice is an independent intervening cause that precludes compensation. *Daniels* v. *New York, etc. Railroad*, 183 Mass. 393, 67 N. E. 424. The physical injury sustained by Barber was not permanent in a physical sense. There was no physical injury of any sort to the brain itself. What happened was that Barber was unable to tolerate the pain, inconvenience and humiliation caused by his physical condition and deliberately chose to end his life. It was a morbid choice but was the deliberate choice of a person of moderately intelligent mental powers, with rational knowledge of the consequences, and the act itself was done with conscious volition. The element of insane frenzy or ungovernable lunacy was wholly absent. The judgment adverse to the widow was accordingly affirmed.

However, in a strong dissent filed by Fowler, Justice, it was argued that the death was the direct "end result" of the injuries sustained in the accident. The condition caused by the accident, this justice said, caused the death. It is of no consequence that the industrial commission found that Barber was conscious that the cutting of his wrists would result in death or that the wounds were not inflicted in a delirium or frenzy without conscious volition. The effect of the bare facts of the case cannot be obviated whether Barber was sane or insane in a medical or psychologic sense or by the commission or the court adopting the view of one or another expert. Nor can such effect be obviated by calling the intervening act an intervening cause when it is not such. The slashing of the wrists was an intervening act but not an intervening cause. An intervening cause is one occurring entirely independent of a prior cause. When a first cause produces a second cause that produces a result, the first cause is a cause of that result. *Kramer* v. *Chicago, M. St. P. & P. R. Co.*, 226 Wis. 118, 276 N. W. 113; *Morey* v. *Lake Superior T. & T. Co.*, 125 Wis. 148, 103 N. W. 271. There is then a direct as distinguished from a broken sequence, and the first cause is a responsible and proximate cause of the result. This seems so plain as not to be set aside by any species of fine spun reasoning. Barber's act in slashing his wrists is no more an intervening cause of his death than is following the advice of a physician who is treating a plaintiff for injuries inflicted by the defendant, when so doing results in a condition to alleviate which the patient must take especial treatment not necessary or appropriate to treatment of his original injury, in which case the expense, loss and suffering caused by the especial treatment proximately result in the defendant's act, such as was held in *Sumner* v. *Kinney*, Texas Civ. App., 136 S. W. 1192. Under the bare facts of this case, in this judge's opinion, the original injuries by direct sequence of causation resulted in death, and liability under the workmen's compensation act follows whenever this sequence appears.

However, because of the opinion of the majority of the court, judgment against the widow was affirmed. *Barber v. Burrell Engineering Co., 6 N. W. (2d) 199 (Wis., 1942).*

Society Proceedings

COMING MEETINGS

American Academy of Ophthalmology and Otolaryngology, Chicago, Oct. 10-13. Dr. W. L. Benedict, 102 Second Ave. S.W., Rochester, Minn., Secretary.

American Congress of Physical Therapy, Chicago, Sept. 8-11. Dr. Richard Kovacs, 2 East 88th St., New York, Secretary.

American Public Health Association, New York, Oct. 12-14. Dr. Reginald M. Atwater, 1790 Broadway, New York, Executive Secretary.

Association of Military Surgeons of the United States, Philadelphia, Oct. 21-23. Colonel James M. Phalen, Army Medical Museum, Washington, D. C., Secretary.

Delaware, Medical Society of, Wilmington, Oct. 12-13. Dr. W. O. La Motte, 601 Delaware Ave., Wilmington, Secretary.

District of Columbia, Medical Society of the, Washington, Sept. 30-Oct. 2. Mr. Theodre Wiprud, 1718 M St. N.W., Washington, Secretary.

Idaho State Medical Association, Boise, Aug. 29-31. Dr. F. B. Jeppesen, 105 North 8th St., Boise, Secretary.

Indiana State Medical Association, Indianapolis, Sept. 28-30. Mr. T. A. Hendricks, 23 East Ohio St., Indianapolis, Executive Secretary.

Kansas City Southwest Clinical Society, Kansas City, Mo., Oct. 4-6. Dr. William M. Korth, 1115 Grand Ave., Kansas City, Mo., Secretary.

Kentucky State Medical Association, Louisville, Oct. 4-6. Dr. P. E. Blackerby, 620 South Third St., Louisville, Acting Secretary.

Michigan State Medical Society, Detroit, Sept. 22-24. Dr. L. Fernald Foster, 2020 Olds Tower, Lansing, Secretary.

Mississippi Valley Medical Society, Quincy, Ill., Sept. 29-30. Dr. Harold Swanberg, 510 Maine St., Quincy, Ill., Secretary.

Oklahoma City Clinical Society, Oklahoma City, Oct. 18-21. Dr. Clark H. Hall, 117 North Broadway, Oklahoma City, Secretary.

Oregon State Medical Society, Portland, Sept. 4-5. Dr. Thomas D. Robertson, St. Vincent's Hospital, Portland, Secretary.

Pennsylvania, Medical Society of the State of, Philadelphia, Oct. 5-7. Dr. Walter F. Donaldson, 500 Penn Ave., Pittsburgh, Secretary.

Wisconsin, State Medical Society of, Milwaukee, Sept. 13-15. Mr. Charles H. Crownhart, 110 East Main St., Madison, Secretary.

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1933 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Hygiene, Baltimore

37:239-340 (May) 1943

Experiment on Range of Dispersion of Anopheles Quadrimaculatus. D. E. Eyles and L. K. Bishop.—p. 239.
Notes on Peruvian Sandflies with Descriptions of Phlebotomus Battistinii, N. Sp., and P. Pescei, N. Sp. M. Hertig.—p. 246.
Notes on Cutaneous Leishmaniasis and Phlebotomus in the Province of Andahualas, Peru. H. Pesce and L. Pardo G.—p. 255.
Studies on Syphilis in Eastern Health District of Baltimore City: I. Principles Concerned in Measuring Frequency of Disease. T. B. Turner.—p. 259.
Id.: II. Discovery Rates as an Index of Trend. T. B. Turner, R. Dyar, E. G. Clark and Mary Footner Birkhead.—p. 273.
Serologic Studies on Mouse Strain of Dwarf Tapeworm, Hymenolepis Nana Var. Fraterna. J. E. Larsh Jr.—p. 289.
*Effect of Subcutaneous Vaccination with Influenza Virus on Virus Inactivating Capacity of Nasal Secretions. T. Francis Jr., H. E. Pearson, R. R. Sullivan and P. M. Brown.—p. 294.
Nomenclature of Pathogenic Rickettsiae. C. B. Philip.—p. 301.
Studies on Reducing Substances and Gas Formation in Cultures of Endameba Histolytica and Single Species of Symbiotic Bacteria. T. von Brand, C. W. Reese, L. Jacobs and Lucy V. Reardon.—p. 310.
*Persistence of Poliomyelitis Virus in Flies. F. B. Bang and R. W. Glaser.—p. 320.
Further Studies of 3T Strain of Plasmodium Cathemerium in White Pekin Ducks. F. Wolfson.—p. 325

Subcutaneous Vaccination with Influenza Virus.—Francis and his co-workers show that the tendency has developed to consider that procedures which increase the level of antibodies enhance resistance in a parallel manner. In the acceptance of such conclusions little consideration has been given to the pathogenesis of the disease or to an explanation of the manner in which circulating antibodies can influence the resistance of the superficial respiratory epithelium which the virus of influenza initially and selectively attacks. The evidence presented by the authors shows that, when subcutaneous vaccination of human subjects with active or inactive influenza virus induces a significant increase in the titer of neutralizing antibodies in the blood, the capacity of the nasal secretions to inactivate the virus is also enhanced. It is suggested that the influence of vaccination on the nasal secretions, rather than on circulating antibodies as such, is the factor which determines the efficacy of vaccination in prevention of the natural disease.

Persistence of Poliomyelitis Virus in Flies.—According to Bang and Glaser, increasing emphasis is placed on the intestinal route of infection by the virus of poliomyelitis. It is natural that attention should again be directed to the role of flies. The authors studied the infection of adults and larvae of the common housefly (Musca domestica), the green-bottle fly (Lucilia lepida [caesar]), the stable fly (Muscina stabulans), the blowfly (Calliphora erythrocephala) and the flesh fly (Sarcophaga hemorrhoidalis). The experiments were not undertaken with the purpose of yielding definitive data on the question of fly transmission of human poliomyelitis but rather to furnish a biologic background for such a study. The different results obtained with the two viruses (Theiler's virus and the Lansing virus) suggest that more work on human viruses must be done. The results are in agreement with the work of Howard and Clark, who in 1912 found that Musca domestica fed on monkey cord infected with a human strain of poliomyelitis would retain the virus for at least forty-eight hours and that this virus might be recovered from the viscera of the fly. The consistently negative attempts to isolate virus from adults when the larvae are infected suggest that infection of larvae in nature is not important in the spread of the virus. The virus may be recovered from the adult fly only when the adult itself is infected by feeding. Theiler's virus may be recovered from Musca domestica as long as twelve days after infection, but the mouse adapted human strain survived only two days in the housefly. The authors were unable to recover the mouse adapted Lansing virus from the four other species tested, while results with the mouse "poliomyelitis" in these species did not differ essentially from those obtained with Musca domestica.

American Journal of Ophthalmology, Cincinnati

26:443-564 (May) 1943

Walter B. Lancaster, M.D. Biographic Sketch and Bibliography 1897-1943. J. J. Regan.—p. 445.
Angiomatosis Retinae (von Hippel's Disease). Results Following Irradiation of Three Eyes. F. C. Cordes and O. C. Dickson.—p. 454.
Orthoptics: Education in Binocular Skill. Julia E. Lancaster.—p. 463.
Lens Extraction Following Filtering Operations for Glaucoma. S. R. Gifford.—p. 468.
Aspects of Brazilian Ophthalmology. M. E. Alvaro.—p. 474.
Study of Anisekonia in Case of Increasing Unilateral Index Myopia. H. M. Burian and K. N. Ogle.—p. 480.
Severe Keratoiritis Due to Brucellosis: Successful Treatment with Brucella Abortus Vaccine. J. Green.—p. 491.
Hereditary Macular Degenerations. R. I. Lloyd.—p. 499.
Comparison of Keratome-Scissors and Graefe Knife Incisions for Cataract Extraction. C. S. O'Brien.—p. 508
Glioma of Retina in Successive Generations. W. L. Benedict and Edith M. Parkhill.—p. 511.
Aniseycloplegia. S. J. Beach.—p. 522.
Concerning Detachment of Retina. H. S. Gradle.—p. 524.
Resection of Left Inferior Oblique Muscle at Its Scleral Attachment for Postoperative Left Hypotropia and Left Pseudoptosis. C. Berens and M. Loutfallah.—p. 528.
Venesection in Case of Choroidal Hemorrhage Following Cataract Extraction. J. J. Regan.—p. 534.
Clinical Applications of Fluorescence in Relation to Melanotic Pigment. T. L. Terry.—p. 536.
Lancaster's Technic of Cataract Extraction. K. L. Roper.—p. 540.
Clearing of Edematous Corneas by Glycerin. D. G. Cogan.—p. 551.
Objectives of Orthoptic Examination and Treatment. A. Linksz.—p. 552.

Annals of Internal Medicine, Lancaster, Pa.

18:719-912 (May) 1943

*Cancer of Stomach, with Special Reference to Early Diagnosis. I. W. Held and I. Busch.—p. 719.
Leaven of Psychosomatic Medicine. E. A. Strecker.—p. 736.
*Severe Injury to Kidneys and Brain Following Sulfathiazole Administration: High Serum Sodium and Chloride Levels and Persistent Cerebral Damage. J. A. Luetscher Jr. and S. S. Blackman Jr.—p. 741.
Leukemia: Relative Incidence of Its Various Forms and Their Response to Radiation Therapy. F. H. Bethell.—p. 757.
Experimental Studies on Heparin and Its Influence on Toxicity of Digitaloids, Congo Red, Cobra Venom and Other Drugs. D. I. Macht.—p. 772.
Sugar Alcohols: XXIV. Metabolism of Sorbitol in Diabetes. F. W. Ellis and J. C. Krantz Jr.—p. 792.
*Ménière's Syndrome and Migraine: Observations on Common Causal Relationship. M. Atkinson.—p. 797.
Arachnoiditis (Diffuse Proliferative Leptomeningitis). A. Blumstein and A. B. Baker.—p. 809.
New Trends in Treatment of Chronic Disease: Experience in Spa Therapy. W. S. McClellan.—p. 825.
Circulatory Disturbances in Prostatic Hypertrophy. M. Mallory, F. Mathers, L. M. Orr 2d and P. R. Kundert.—p. 835.
Some Probative Aspects of Early Germanic Codex, Carolina and Bambergensis. S. Pilsky and S. Berresford.—p. 841.

Early Diagnosis of Cancer of Stomach.—Held and Busch divide cases of cancer of the stomach into two groups: those in which the cancer develops in a healthy gastric mucosa and those in which the cancer develops on a previously diseased mucosa. Approximately 70 per cent of all cases belong to the first group. The slowly growing cancers that develop on a healthy gastric mucous membrane should be operated on even if a large palpable mass is present, because they do not exhibit a tendency to early metastasis. Lasting and good results may be expected. Without operative intervention the mortality is 100 per cent. It is difficult to foretell the percentage of five year survivals or even cures in the aforementioned groups, but in the absence of metastases and with a successful operation the patient can go on for many years without recurrence. The medullary form of carcinoma of the stomach usually arises on a previously healthy mucous membrane, grows very rapidly and has a tendency to early metastasis. The group in which the cancerous lesion develops on a previously diseased mucous membrane comprises 30 per cent of all cases, and gastric complaints were present for many years before cancer developed,

while in others the growth of the cancer is so slow that the lesion remains localized for several years. The precancerous symptoms vary and are usually bizarre and noncharacteristic and are therefore interpreted mostly as neurogenic. There are three separate groups of clinical entities on the soil of which the cancer develops: (1) gastritis, (2) polyps and (3) gastric ulcer. Gastroscopy has materially increased the percentage of early diagnosis of cancer. Cancer which develops on a previously diseased mucous membrane, as in the case of gastritis, polyposis or gastric ulcer, has a tendency to grow much slower, is more benign and, when diagnosed early, offers a chance for prolongation of life and even permanent cure. Individuals with ulcer symptoms without ulcer signs should be looked on with greater suspicion and more watchfulness for early cancer than those in whom ulcer is clinically and roentgenologically demonstrable. A high degree of anemia and the size of the palpable mass should not deter one from operative intervention, provided preoperative and postoperative treatment are carried out with the greatest care.

Sulfathiazole Injury to Kidneys and Brain.—Luetscher and Blackman give detailed histories of 3 patients with severe sulfathiazole intoxication and of 2 patients with probable sulfonamide poisoning. All the patients developed an unusual increase in serum sodium and chloride concentration. When continuous observations were made, the electrolyte disturbance appeared while oliguria and nitrogen retention diminished. The excessive height of the serum electrolyte concentration probably contributed to the death of 2 patients. The renal lesions found in 2 cases suggest that the dissociation of salt and water excretion may be related to changes in certain specific portions of the tubule. There were thrombi in the interlobular veins in 2 cases. In 1 of these, thrombi in both interlobular arteries and veins were numerous and probably produced the renal lesions. In both cases the thrombosed veins were associated with ruptured tubules and the proliferation of tubular epithelium in the thrombi. Both patients developed moderate hypertension. Clinically there was evidence of cerebral damage. In the 2 patients who survived the uremia and hyperchloremia, signs of injury to the central nervous system persisted with slow and incomplete recovery. In the examined brains areas of edema and gliosis were found together with small hemorrhages in 1 case.

Ménière's Syndrome and Migraine.—In an earlier report Atkinson demonstrated that cases of Ménière's syndrome can be divided into two groups by means of an intradermal histamine test. There is a small group which is sensitive to histamine and which presents a primary vasodilator or allergic basis. This group can be satisfactorily treated by desensitization to histamine or by elimination of the specific antigen. In a second group, which constitutes the large majority, there is no sensitivity to histamine and the attacks are the result of a primary vasospasm. In this group relief can generally be obtained by administration of vasodilator drugs, of which the most satisfactory is nicotinic acid. In migraine also there is evidence of a dual etiology of the same nature as in Ménière's syndrome. Allergy as a cause of migraine attacks has been generally accepted as applying to at least a portion of the cases. On the other hand, Wolff and his collaborators have shown that migraine attacks can be the result of a primary vasospastic process. Thus the syndrome of Ménière and migraine are identical as far as the mechanism of their production is concerned. They differ in the location of the impact—in the one case it is on the labyrinth, in the other on the cerebral hemisphere. What determines location or laterality is not apparent. The two syndromes differ too in the frequency of occurrence of the two groups. Whereas in Ménière's syndrome the primary vasodilator group is a relatively small one compared with the vasoconstrictor, in the migraine syndrome the position, if not reversed, is at least more nearly equal. Allergy as a cause of migraine is common, as a cause of paroxysmal vertigo is uncommon. This fits in with the age groups in which the two syndromes arise—paroxysmal headache is a condition of youth, like the vasodilatation which produces it, paroxysmal vertigo a condition of middle life or later, like the vasoconstriction which is its usual cause. Nicotinic acid is used in the treatment of the vasoconstrictor group not because it is a part of the vitamin B complex but because it is a powerful capillary vasodilator. It is this basic vascular mechanism which presumably explains the satisfactory results reported with such divergent substances as thiamine hydrochloride and estrogens—both have a certain vasodilator action apart from their specific replacement function. The author directs attention to the frequent association of migraine and Ménière's syndrome. He encountered migraine in 22 of 108 cases of Ménière's syndrome. Migraine attacks have been known to merge into Ménière attacks. Treatment which has proved successful in relieving the vertigo of patients with Ménière's syndrome has also relieved the migraine headache in those cases in which it also has been present. Treatment of this syndrome, whether characterized in the main by vertigo or by headache, to be successful depends on accurate grouping of cases. No single method will achieve success in all cases, for there is more than one cause.

Annals of Surgery, Philadelphia

117:641-800 (May) 1943

*Lobectomy for Pulmonary Tuberculosis. E. D. Churchill and R. Klopstock.—p. 641.
Local Effect of Sulfanilamide, Sulfathiazole and Sulfadiazine on Hemolytic Staphylococcus Aureus Infections of Pleural Cavity. R. A. Daniel Jr., F. T. Billings and R. R. Crutcher.—p. 670.
Effect of Sulfanilamide, Sulfathiazole and Sulfadiazine on Peritoneum. R. R. Crutcher, R. A. Daniel Jr. and F. T. Billings.—p. 677.
*Prevention of Shock and Death by Immediate Application of Pressure Dressing to Severely Frozen Limbs of Dogs: Experimental Study. E. H. Fell and R. Hanselman.—p. 686.
Blood Circulation in Pedicle Flaps: Accurate Test for Determining Its Efficiency. B. Douglas and R. R. Buchholz.—p. 692.
Perforated Peptic Ulcer. F. X. Timoney.—p. 710.
Atresia of Duodenum: Case Successfully Treated by Duodenoduodenostomy. C. S. Ward Jr. and F. W. Cooper Jr.—p. 718.
Congenital Atresia of Common Bile Duct: Case Report. A. Strauss, J. Gross and S. Kyman.—p. 723.
Cyst of Ampulla of Vater: Case Report. B. Brooks and A. Weinstein.—p. 728.
Hyperesthesia of Posterior Peritoneum (Objective Pain) in Appendicitis and Other Visceral Lesions. R. Capurro.—p. 735.
Metabolic Studies in Patients with Cancer of Gastrointestinal Tract. I. Ariel, Florence Jones, G. T. Pack and C. P. Rhoads.—p. 740.
Treatment of Postoperative Hypoproteinemia in Patients with Cancer of Colon and Rectum. G. E. Binkley, J. C. Abels and C. P. Rhoads.—p. 748.
Accessory Spleen in Scrotum: Review of Literature on Ectopic Spleens and Their Associated Surgical Significance. J. M. Emmett and M. L. Dreyfuss.—p. 754.
Spontaneous Rupture of Urinary Bladder: Report of Case of Second Rupture. W. B. Marbury and W. Fry.—p. 760.
Preoperative Scrubbing in Abdominal Surgery: II. Clinical Studies. J. K. Berman.—p. 766.
Clinical Uses of Vitallium. C. S. Venable and W. G. Stuck.—p. 772.

Lobectomy for Pulmonary Tuberculosis.—Churchill and Klopstock report lobectomies performed for pulmonary tuberculosis. All of the patients had positive sputum. A preoperative diagnosis of tuberculosis was made in every instance. Resection of upper lobes by individual ligation technic have been routinely practiced at the authors' hospital since 1936 and total 21 in number. In this paper they review 6 cases; 3 presented orthodox indications for resection of the lesion by lobectomy. Three others presented the usual indications for thoracoplasty, but lobectomy was performed instead. Primary healing took place in all instances. Lobectomy provides a more selective and immediate method of eradicating certain tuberculous lesions than does collapse therapy. It may be resorted to subsequent to artificial pneumothorax.

Prevention of Shock and Death by Pressure Dressing.—Fell and Hanselman anesthetized 10 dogs with pentobarbital sodium and maintained them under light anesthesia for ten to twelve hours. The right hind extremities were immersed to the upper third of the thigh in a mixture of solidified carbon dioxide and 95 per cent alcohol, at — 55 C. for twenty minutes. The entire portion was frozen within two minutes. Five of the dogs received no treatment and their legs were allowed to thaw out at room temperature. To the frozen hind legs of the other 5 dogs two to three layers of sheet wadding were applied and over this a plaster encasement. All 5 of the untreated dogs developed clinical shock, 4 of them dying within thirteen hours. All the treated dogs lived. The maximum increase in the hematocrit was only about half as great as in the untreated group. The thawing out of the encased legs was extremely slow; they were cold and moist for twelve hours or longer. The plaster encasement affords a firm, even pressure

splintage and allows for slow thawing. Four of the 5 treated dogs developed necrotic limbs. Two dogs had their necrotic infected extremities amputated eight and eleven days after freezing and made uneventful recoveries. Another dog had his leg amputated forty-eight hours after freezing and likewise recovered. The authors think that pressure dressing could be applied to frozen, compressed or burned parts. The time for such application is before the swelling sets in; immediately after the limb has been released from the crushing load, directly after the burn, and before any thawing of the frozen part has taken place.

Archives of Pathology, Chicago

35:787-942 (June) 1943

Effects of Intravenous Injections of Ether Insoluble Fraction of Lipoids of Beef Brain: Comparison with Lipoid Storage Diseases and with Effects of Injections of Phosphatides Alone. Edna H. Tompkins.—p. 787.
Cellular Origin of Bronchial Adenoma. A. P. Stout.—p. 803.
Bacillus Coli Pneumonia. I. N. Dubin and G. P. Kerby.—p. 808.
Congenital Aneurysms of Cerebral Arteries: Embryologic Study. J. L. Bremer.—p. 819.
Epicellular and Pericellular Depositions of Amyloid as Starting Point of Amyloidosis. J. T. Peters.—p. 832.
Epinephrine and Related Substances in Human Arterial Walls and Kidneys: Their Role in Arteriosclerosis. W. Raab.—p. 836.
Experimental Studies in Cardiovascular Pathology: VII. Chronic Nicotine Poisoning in Rats and in Dogs. W. C. Hueper.—p. 846.
Studies in Vitro on Physiology of Normal and of Cancerous Cells: I. Effect of High Temperature and of Moccasin Venom on Viability of Rabbit Lymphocytes and Polymorphonuclear Leukocytes as Determined by Method of Unstained Cell Counts. R. Schrek.—p. 857.
Pinealoma: Clinicopathologic Study of 7 Cases with Review of Literature. W. O. Russell and E. Sachs.—p. 869.
Acute Ulceration of Esophagus with Associated Intranuclear Inclusion Bodies: Report of 4 Cases. J. Pearce and A. Dagradi.—p. 889.

Indiana State Medical Assn. Journal, Indianapolis

36:283-330 (June) 1943

Industrial Hygiene in War Production. J. J. Bloomfield.—p. 283.
Organization of Medical Services in Industry. E. C. Hornblad.—p. 289.
Fatality Following Neoarsphenamine Therapy. M. Miller.—p. 292.
*Brucellosis: Report of 53 Cases with an Introductory Report on Intradermal Vaccine Therapy. D. L. Urschel.—p. 294.
*Prevention and Treatment of Postoperative Pulmonary Atelectasis by Stir Up Regimen and Tracheobronchial Toilet. W. B. Adams.—p. 299.
When Should Blood Test Be Taken During Pregnancy? S. R. Mercer.—p. 301.
Syphilis Control in Industry. H. A. Vonachen.—p. 302.

Brucellosis.—The chronic phase of brucellosis is often overlooked. Doctors practicing in rural districts or in towns where pasteurization of milk is not legally required should always consider this disease in diagnosing chronic illness. Urschel tested 124 patients with suggestive histories for brucellosis by means of intradermal vaccine. Seventy of these, or 56.4 per cent, gave a positive skin reaction to the Brucella abortus and Brucella suis vaccine. Fifty-three, or 42.8 per cent, were considered to have clinically active brucellosis. Only 2 children were encountered with the condition. The average age of the patients was 41. Twenty-three per cent of the active cases gave a history of exposure to Bang's disease in cattle. All these patients consumed raw milk. Forty-three per cent of the active cases gave a past history of febrile illness suggestive of brucella infection. Tiredness was the most common symptom. Other symptoms were headache, weight loss, weakness, nervousness, fever, constipation, bloating and chest pain. The number of positive agglutination reactions prior to treatment was low. The hematocrit reading showed a high average volume of packed red cells; otherwise the laboratory findings were not significant. Most of these patients were treated with subcutaneous or intradermal administration of vaccine or with a combination of the two. Of the treated patients 88.7 per cent improved, while 11.3 per cent did not improve. There was little difference in the results of subcutaneous and intradermal vaccine therapy. The latter method has value when unexpected febrile responses occur from subcutaneous vaccine treatment. It remains to be proved whether the antibody response varies in the two methods.

Pulmonary Atelectasis.—Bronchoscopic aspiration is the recognized treatment of postoperative pulmonary atelectasis, but the method is not readily available in many hospitals. The stir up regimen so widely advocated by Waters helps prevent atelectasis in the postoperative period. It consists of three points: 1. The patient must radically change his position. 2. He must cough vigorously. 3. He must take several deep breaths. For the tracheobronchiai toilet the anesthetist can introduce a soft rubber tube between the vocal cords and aspirate the tracheobronchial tree. The tracheobronchial toilet is useful when the patient is too weak or too depressed to cough out the pulmonary secretions, which will accumulate and prevent adequate oxygen exchange. This is seen after cerebral accidents or brain operations. Prompt drainage is of value, and repeated aspirations may be necessary.

Journal of Experimental Medicine, New York

77:487-594 (June) 1943

Immunity to Yellow Fever Encephalitis of Monkeys and Mice Immunized by Neural and Extraneural Routes. J. P. Fox.—p. 487.
Nonfatal Infection of Mice Following Intracerebral Inoculation of Yellow Fever Virus. J. P. Fox.—p. 507.
Venezuelan Equine Encephalomyelitis in Man. J. Casals, E. C. Curnen and L. Thomas.—p. 521.
Detection of Poliomyelitis Virus in Flies Collected During Epidemics of Poliomyelitis: I. Methods, Results and Types of Flies Involved. J. D. Trask, J. R. Paul and J. L. Melnick, with technical assistance of J. T. Riordan and M. Bishop.—p. 531.
*Id.: II. Clinical Circumstances Under Which Flies Were Collected. J. D. Trask and J. R. Paul.—p. 545.
Influence of Biotin on Susceptibility to Malaria. W. Trager.—p. 557.

Poliomyelitis Virus in Flies.—During the summer and fall of 1941 Trask and Paul collected 19 samples of flies in epidemic areas both during and after epidemics of poliomyelitis. Of 8 samples collected for the most part during the latter part of a local epidemic but within ten days of the onset of a local case of poliomyelitis 4 yielded the virus, whereas of 8 samples collected more than ten days from the onset of the last local case none yielded the virus. In 4 instances there was a potential though not proved source of virus in the form of "exposed" human feces of recent origin within a few yards or few feet of the site where flies were collected. Collections of flies from three of these sites yielded the virus.

Journal of Immunology, Baltimore

46: 263-346 (May) 1943

*Persistence of Leptospira Antibodies in Circulating Blood of Patients Recovered One to Over Twenty Years from Weil's Disease. A. Packchanian and N. Tom.—p. 263.
Quantitative Methods in Study of Phage-Antiphage Reaction. A. D. Hershey, G. Kalmanson and J. Bronfenbrenner.—p. 267.
Immunizing Potency in Man of Purified Antigenic Material Isolated from Eberthella Typhosa. H. R. Morgan, G. O. Favorite and J. A. Horneff.—p. 301.
Comparison of Antigenic Properties of Staphylococcus Vaccine, Staphylococcus Toxoid and the Two in Combination. S. Etris.—p. 309.
*Staphylococcus Vaccine-Toxoid Combined in Human Immunization. F. B. Faust and S. Etris.—p. 315.
Complementary Activity of Mouse Serum. G. C. Brown.—p. 319.
Antigenic Properties of Mouse Tissues. G. C. Brown.—p. 325.
Biologic Assay of Tetanus Toxoid. L. Greenberg, C. A. Morrell and J. Gibbard.—p. 333.
Effect of Temperature of Inactivation of Human, Rabbit and Guinea Pig Serum on Hemolytic Activity of Complement. Elizabeth L. Hazen.—p. 341.

Persistence of Leptospira Antibodies.—According to Packchanian and Tom, laboratory and clinical data are available to prove that patients suffering from Weil's disease produce specific antibodies against Leptospira icterohemorrhagiae and that the presence of such antibodies can be demonstrated in the circulating blood by serologic and immunologic tests. These antibodies may persist in the patient's blood for a long time after complete recovery, thus making possible a retrospective diagnosis. Eight persons who had recovered from Weil's disease from two to over twenty years still had agglutinins for type I Leptospira icterohemorrhagiae present in their circulating blood in significantly high titer. The average level of agglutinative titer during the active phase of the disease in 7 cases was 1:23,000. The minimal dilution in which agglutination occurred between two and twenty years after complete recovery was 1:100, while the maximal was over 1:30,000.

Staphylococcus Vaccine-Toxoid.—Faust and Etris report that normal individuals receiving ten injections of staphylococcus vaccine-toxoid combined (Vatox) showed a decided increase in both agglutinins and antitoxin. The average increase of agglutinins was fifty-seven fold and the average antitoxin increase tenfold when compared with the preinjection levels. Patients with known or suspected staphylococcic infec-

tion were on an average less responsive to antibody stimulation than the normal group, although after vaccination the serum of the patient with staphylococcic proctitis contained agglutinins and antitoxin in greater quantity than the average of the normal individuals. The use of staphylococcus vaccine-toxoid combined is a logical approach to the dual stimulation of antibacterial and antitoxic substances in the treatment of staphylococcic infections.

Journal of Lab. and Clinical Medicine, St. Louis

28:927-1052 (May) 1943

Blood Pressure Fluctuations in Bronchial Asthma: I. Clinical Observations. H. Osgood.—p. 927.
U Wave Patterns in Abnormal Electrocardiogram. S. D. Solarz and S. R. Elek.—p. 936.
Inactivation of Vaccinia Virus by Mild Antiseptics. W. B. Dunham and W. J. MacNeal.—p. 947.
Comparative Effectiveness of Arsenical Compounds and Sulfonamide Drugs Against Bacterial Infections. E. E. Osgood.—p. 953.
Evaluation of Antiseptics and Other Anti-Infectious Agents. W. J. MacNeal and Nancy C. Farnsworth.—p. 963.
Spontaneous Rupture of Spleen Due to Acute Leukemia or Acute Leukemia Due to Trauma to Spleen . . . Which Report of Case and Review of Literature. A. S. Rubnitz, with Collaboration of E. B. Floersch.—p. 972.

Journal-Lancet, Minneapolis

63:121-160 (May) 1943

Pneumonia in Infancy: Pathogenesis and Pathology. J. M. Adams.—p. 121.
Acute Bacterial Meningitis. R. Alway and E. S. Platou.—p. 125.
Old Problems in New Settings. E. K. Clarke and R. A. Jensen.—p. 129.
Gastric Ulceration Complicating Erythroblastosis Fetalis. Rena Crawford and C. A. Stewart.—p. 131.
Experience with Hematogenous Osteomyelitis in Children at the University of Minnesota Hospitals. C. Dennis.—p. 134.
Responsibilities of Physician in Problems of Rheumatic Fever in Children. A. E. Hansen.—p. 138.
Problems and Control of Dental Caries in Children. J. W. Knutson and W. D. Armstrong.—p. 142.
Chronic Constrictive Pericarditis. W. Sako, J. Fleet and P. Pizzalato.—p. 147.
*Early Diagnosis of Poliomyelitis. A. V. Stoesser.—p. 149.

Early Diagnosis of Poliomyelitis.—Recent interest in the Kenny treatment has made the early diagnosis of poliomyelitis important, since the treatment gives its best results when instituted as soon as muscle spasms appear. Stoesser presents a table of the early symptoms that were observed in a careful study of 259 acute cases admitted to the Minneapolis General Hospital during the past six years. The majority were children ranging in age from 1 to 14 years with the highest incidence appearing between 5 and 9 years. The average course of the disease was found to fall into the following phases: (1) fever, headache, nausea and vomiting, restlessness or irritability; (2) continued headache, stiff neck, pain on flexion of neck or spine, muscle pain especially on motion; (3) continued pain on flexion of neck and spine, drowsiness, muscle spasm and no motion. Spinal fluid examination may reveal little if the fluid is collected during the first phase, but during the second and third phases characteristic changes appear which may confirm the diagnosis. Some of the symptoms and signs may be more severe in 1 case than in another and lead to various types of onset—meningeal or cerebral, gastrointestinal and respiratory. Many diseases have been confused with poliomyelitis chiefly because some of their symptoms resemble the characteristic features of the various types of poliomyelitis. This is particularly true of acute upper respiratory infections. If no loss in muscle function occurs and a spinal fluid examination is normal, the diagnosis of poliomyelitis may be dropped. Meningitis may easily be confused with infantile paralysis. Occasionally a rather mild pharyngitis or tonsillitis will be followed by a symmetrical and bilateral loss of muscle function in the extremities. Although poliomyelitis is considered, this diagnosis is questioned because the motor impairment does not have the localized and asymmetrical distribution noted frequently in poliomyelitis. The onset of pneumococcic pneumonia in young children can simulate poliomyelitis. Encephalitis may be confused with the cerebral type of poliomyelitis when the latter progresses rapidly to the third phase and leads to extreme drowsiness. Careful inspection and palpation of the muscles, as recommended by Miss Kenny, reveal muscle spasm early in the course of the disease.

Public Health Reports, Washington, D. C.

58:689-720 (April 30) 1943

Studies of Acute Diarrheal Diseases. A. V. Hardy, W. Burns and Thelma DeCapito.—p. 689.
Species of Fleas on Rats Collected in States West of 102d Meridian and Their Relation to Dissemination of Plague. F. M. Prince.—p. 700.

58:721-756 (May 7) 1943

Rocky Mountain Spotted Fever: Spontaneous Infection in Tick Amblyomma Americanum. R. R. Parker, G. M. Kohls and E. A. Steinhaus.—p. 721.

Rhode Island Medical Journal, Providence

26:51-64 (April) 1943

Bleeding in Head Following Injury: Some Unusual Examples. W. Pickles.—p. 51.

26:65-78 (May) 1943

Inhalation Therapy. M. Sahlad, E. Sahlad and Priscilla Sellman.—p. 65.

Southern Medical Journal, Birmingham, Ala.

36:393-466 (June) 1943

*Control of Endemic and Epidemic Diarrhea: Preliminary Report. D. M. Kuhns.—p. 393.
Postarsphenamine Lichen Planus-like Exanthem. M. H. Goodman and M. Sullivan.—p. 401.
Result of Meniscectomy (Knee Joint) in Soldiers. A. S. Hamilton and H. E. Finklestein.—p. 406.
Cholecystography: Correlation of Roentgenologic, Surgical and Medical Findings in 355 Cases. H. J. Walton and C. N. Davidson.—p. 411.
Treatment of Amenorrhea with Progesterone and Anhydrohydroxyprogesterone. W. M. Allen and S. D. Soule.—p. 415.
Tuberculosis of Reproductive Organs of Women. W. N. Jones.—p. 420.
Influence of War on Obstetrics. H. Jenkins.—p. 422.
Coronary Artery Disease. W. Baumgarten.—p. 426.
Review of Hematology in 1942. R. R. Kracke.—p. 429.
Patch Tests: Their Practical Applications and Limitations. L. H. Warren.—p. 435.
Pellagra Developing in Patient Receiving Liver Extract Parenterally for Sprue. O. C. Hansen-Pruss.—p. 440.
Resistance to Diseases in Childhood. B. B. Jones.—p. 442.
Compound Fractures of Skull. C. C. Coleman.—p. 449.
Ureteritis Complicating Nephroptosis. R. Bell.—p. 451.
Development of Esophageal Speech After Laryngectomy. E. T. Gatewood.—p. 453.
Public Health Hazards in Rural Communities. C. F. McClintic and A. M. Price.—p. 455.

Control of Endemic and Epidemic Diarrhea.—Control of diarrhea and dysentery is a major concern of armies in training and on combat duty. The high incidence of diarrhea in army troops on maneuvers during 1941 and the sporadic recurrence of outbreaks in 1942 have indicated the danger of similar outbreaks occurring under combat conditions. Efforts have been made to acquaint troops in training with proper control and sanitary methods. In order to establish proper preventive and control measures for diarrheal diseases all cases of diarrhea should be examined for the specific etiologic agent. The following laboratory procedures should be carried out in every case of diarrhea: (*a*) A swab culture of the rectal mucosa for pathogenic bacteria which is inoculated directly into inhibitive and differential mediums at the bedside of the patient. (*b*) Direct microscopic examination of the stool to determine the type of exudate, the cellular constituents and the other diagnostic criteria. (*c*) Direct microscopic examination of the stool for parasites. The Hardy swab method of culturing by use of the rubber catheter and swab and improved inhibitory mediums have simplified and made available a more accurate method of obtaining positive cultures. The predominating enteric pathogens isolated and identified in the Fourth Service Command Laboratory during the past year were found to be members of the genus Shigella (99 per cent). Sulfaguanidine and succinylsulfathiazole were used to treat 244 persons with acute bacillary dysentery or convalescing from it, and 182 of these were available for culture following treatment. All were negative by the swab method of culture on one to three follow-up cultures. Cultures from 60 control cases in which treatment was not given were found to be positive at a similar length of time following recovery from dysentery. The culturing of flies and the improved inhibitory mediums present a new application of bacteriologic methods in the determination of the transmitting agent in bacillary dysentery.

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FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

British Journal of Radiology, London

16:157-186 (June) 1943

Erythroblastic Anemia with Review of Literature. J. M. Flynn.—p. 157.
Some Results of Photographic Estimation of Stray X Radiation Received by Hospital X-Ray Personnel. L. H. Clark and D. E. A. Jones. —p. 166.
Radiologic Sign of Pyloric Stenosis. A. S. Johnstone.—p. 169.
Effect of X-Rays on Aqueous Solutions of Biologically Active Compounds. W. M. Dale.—p. 171.
Radiologic Diagnosis of Disproportion. R. Williams.—p. 173.

British Medical Journal, London

1:655-684 (May 29) 1943

Treatment of Pernicious Anemia with Experimental Proteolyzed Liver Preparation: Preliminary Observations. L. J. Davis, L. S. P. Davidson, D. Riding and G. E. Shaw.—p. 655.
Relation of Sunlight to Desert Sores. J. M. Henderson.—p. 657.
Lymphogranuloma Inguinale (Tropical Bubo). F. A. R. Stammers. —p. 660.
Arsenical Encephalopathy: Complication Occurring During Treatment of Syphilis. R. B. Nelson, C. McGibbon and F. Glyn-Hughes.—p. 661.
Hemorrhagic Encephalopathy Following Arsenical Therapy: Case. J. P. A. Halcrow.—p. 663.
Ethyl Chloride Analgesia. J. D. Rochford and B. T. Broadbent.—p. 664.

Medical Journal of Australia, Sydney

1:385-410 (May 1) 1943

*Immunization Against Epidemic Influenza with Living Attenuated Virus. F. M. Burnet.—p. 385.
*Experimental Immunization of Volunteers Against Influenza Virus B. Diana R. Bull and F. M. Burnet.—p. 389.
*Intranasal Vaccination of Humans with Living Attenuated Influenza Virus Strains. Jessica Mawson and C. Swan.—p. 394.

Immunization Against Epidemic Influenza with Living Virus.—The method of immunization used by Burnet was to spray into each nostril egg fluid containing a high concentration of three living attenuated strains of influenza virus representing the main antigenic types. About 0.25 cc. of virus was used for each subject. The proportion of persons showing a rise in antibody level is greatest among those having the lower initial antibody levels. Of the 91 subjects whose serum was fully tested, 46 showed a rise regarded as significant against one or more components of the vaccine. These results are considerably inferior to those obtained by American workers with subcutaneous inoculations; but the intranasal vaccine can be expected to take only in subjects susceptible to influenza virus infection. In the pandemic of 1918 about 70 per cent of persons escaped clinical infection. Even with an "ideal" vaccine of this type, one would not expect more than 30 to 50 per cent of subjects to show a definite rise in antibody level against any one type. In one unit of about 7,000 men it was possible to obtain information as to the effect of immunization on the incidence of respiratory tract infection during a proved influenza epidemic. Immunization was being carried on in this unit during the period of influenza prevalence, and only two weeks were available in which (*a*) the immunized group had been inoculated more than one week previously and (*b*) the influenza epidemic was still current. During these two weeks 4.4 per cent of the immunized "reported sick" with some form of upper respiratory tract infection, as against 6.63 per cent of those not immunized. This apparent 50 per cent advantage of the immunized must be treated with reserve. There was at most only a minor benefit in this epidemic. The intranasal method has disadvantages and potential dangers. The possibility that the immunizing infection will exacerbate an infection in the nasal sinuses must be considered.

Immunization Against Influenza Virus B.—Bull and Burnet have consistently found that results with influenza virus B are more regular than those obtained with type A strains. The level of circulating antibody (Hirst's method) is a fairly accurate index of susceptibility to experimental infection with living attenuated influenza virus B. The authors tested some modifications in the method of administering the virus and determined whether a primary administration of virus produced resistance to a second administration some months later. A blood sample was taken from about 100 volunteers to select those whose serum tested by Hirst's method had a low antibody level against influenza virus B. The virus was administered in the form of allantoic fluid from embryos inoculated with the thirty-ninth amniotic passage of influenza virus B. Twenty-three volunteers with a low level of influenza virus B antibody were inoculated intranasally with attenuated influenza virus B and after three to six months received a second similar inoculation. There are indications that the procedure may provide a substantial protection against natural influenza B by showing that a subsequent inoculation produces a much lower proportion of antibody responses and of virus reisolations than the first series. It indicates the complexity of the problems of influenza, however, when it is considered that the proportion of minor symptoms was greater after the second inoculation than after the first. Twenty-one members of the group showed a significant rise in antibody level after the first administration; only two members did so after the second. Some evidence has been obtained that allergic factors play a part in the production of symptoms.

Intranasal Vaccination with Living Influenza Virus.—Mawson and Swan treated one hundred volunteers with a single dose of virus. The vaccine consisted of pooled allantoic fluids from chicken embryos infected with the W. S. and Melbourne strains of influenza virus A and with the Lee strain of influenza virus B. Up to the time of writing (five months after vaccination) no epidemic of influenza had occurred in the community. The efficacy of the vaccine, therefore, has yet to be tested. The authors also investigated the effect of repeated vaccination on volunteers who showed no antibody response to the first spraying. They conclude that, as far as antibody increase is considered, the administration of living, attenuated influenza virus strains by nasal spray appears to have no advantage over the subcutaneous injection. There is a possibility that the resultant mild infection of nasal tissues will lead to an increase in local resistance not obtained by subcutaneous injection. Although the average increase in antibody against each of the three strains in the vaccine was approximately twofold, the individual responses varied from no increase to a twenty-seven-fold increase. Unless all those subjects showing no increase in antibody were already immune, those people would be a source of danger in a community in which large scale vaccination was relied on in an epidemic. Repeated vaccination failed to raise the antibody levels in the majority of cases. It is probable that they fall in the 50 to 90 per cent of people who do not contract influenza even in pandemic periods and that, conversely, the people responding to the nasal vaccine will be just those who will prove susceptible to a respiratory infection like influenza.

1:411-432 (May 8) 1943

*Experimental Mumps: Transmission of Disease to Monkeys: Attempts to Propagate the Virus in Developing Hen's Eggs. C. Swan and Jessica Mawson.—p. 411.
Congenital Abnormalities, Teratology and Embryology: Some Evidence of Primitive Man's Knowledge as Expressed in Art and Lore in Oceania. I. Brodsky.—p. 417.

Experimental Mumps in Monkeys: Attempts to Propagate the Virus in Hen's Eggs.—Swan and Mawson collected saliva from 36 patients, usually within twenty-four hours of the onset of parotitis. They inoculated the saliva into monkeys, but only the last 3 of 14 experiments were successful. All 3 positive results were obtained from a specimen of saliva which comprised the pooled saliva collected from 4 patients within four to twelve hours of the onset of parotitis. The incubation period in these animals was ten, thirteen and sixteen days respectively. By injecting suspensions of the excised parotid glands of the animals thus affected into further monkeys, it was possible to transmit the disease in three passages. The incubation period in the passage animals was five or six days. By the use of specimens of the cerebrospinal fluid of 4 patients suffering from mumps meningoencephalitis, six attempts were made to isolate the virus. Positive results were obtained from only 1 of the 4 patients. In this case again passage succeeded in several monkeys. Two of eight attempts to cultivate the virus of mumps in developing hen's eggs gave suggestive, but not necessarily positive, results. Rabbits, mice, guinea pigs and dogs remained well when inoculated with mumps virus by various routes.

Ophthalmologica, Basel

103:1-64 (Jan.) 1942. **Partial Index**

*Keratoplasty in Serpiginous and Other Ulcers of Cornea. E. A. Tschetschik-Kunina.—p. 1.
Causes of High Vitamin C Concentrations in Aqueous Fluid and Lens. J. H. B. M. Huysmans and F. P. Fischer.—p. 21.
Nonirritating Eye Drops. H. M. Dekking and J. P. Bylveld.—p. 40.

Keratoplasty in Serpiginous and Other Ulcers.—Tschetschik-Kunina employed penetrating keratoplasty in the treatment of 15 patients with serpiginous ulcer of the cornea (mostly pneumococcic). The results were satisfactory. Pain and inflammation ceased and infiltration and opacity quickly subsided. In three fourths of the severe cases the eye was saved and in half of these visual acuity was satisfactory. Opacity of the transplant and formation of anterior synechia, eventually with increased pressure, were complications. The author is of the opinion that if the operation was extended to less severe cases the results would be even better. The nonpenetrating lamellar keratoplasty is inadequate.

Revista Clínica Española, Madrid

8:143-218 (Feb. 15) 1943. **Partial Index**

Relation Between Intracranial Diseases and Gastroduodenal Ulcer. H. G. Mogena.—p. 143.
*Spinal and Cerebral Hydatidosis. A. Ley and J. Pons Tordera.—p. 181.
Syphilis of Esophagus. J. Corona Postigel.—p. 199.
Vitaminized Oils in Therapy of Burns. J. García-Sala.—p. 201.

Cerebral and Spinal Hydatidosis.—Ley and Pons Tordera observed 3 cases of cerebral hydatidosis and 1 of spinal involvement among two groups of 200 intracranial tumors and 30 extramedullary spinal tumors. The patients in the first group were 2 women and a boy of 11 years. The clinical and neurologic symptoms were those of a benign intracranial tumor. Acute focal symptoms were present in all. The cerebrospinal fluid was normal. The operation consisted in a craniectomy, extirpation of the cyst and the membranes and irrigation of the operative field with a weak formaldehyde solution. The cysts proved to be primary and solitary in all of the cases. They were located in the posterior cerebral fossa in 2 cases and in the frontoparietal lobe in 1 case. The Weinberg and Cassoni tests performed after the operation gave a negative result in 2 cases and a slightly positive in 1. Eosinophilia was not observed. The cyst recurred in 2 cases. Extirpation of the recurrent cyst has been successful thus far four years and one year respectively after the operation. The patient with spinal hydatidosis showed symptoms and x-ray signs of medullary compression in the dorsal region. A hydatid cyst was found during the operation. It was successfully removed.

Deutsche medizinische Wochenschrift, Leipzig

68:133-156 (Feb. 6) 1942. **Partial Index**

Development of Intestinal Toxins in Intestinal Autointoxication. E. Becher.—p. 133.
*Control of Diphtheria Immunity Several Years After Immunization. F. Faragó.—p. 137.
Is Hepatic Function Impaired by Vaccination with Bacterial Vaccines? (Treatment with Sulfonamides.) H. Wilde.—p. 139.
Hypertension as Cerebral Function. A. Sturm.—p. 141.
Casuistics on Arsphenamine Encephalitis. R. Tidow.—p. 146.

Diphtheria Immunity.—Faragó says that immunization against diphtheria has been obligatory in Hungary since January 1938. It is induced with a toxoid precipitate during the second and seventh years of life. He investigated the question whether immunization with 1 cc. of precipitate during the second year of life conferred adequate protection until the seventh year. The Schick test was performed on 23,393 immunized children. On the basis of these studies and on epidemiologic observations Faragó concluded that immunization with toxoid precipitate has proved its value. The natural antigen stimulus, the latent infection, plays its part. A single immunization is adequate as long as the present epidemiologic conditions prevail. Presumably, as the immunity increases, the latent infection will decrease in the course of years. If later the basic immunity of children should decrease, the adequacy of a single immunization may again have to be tested.

Klinische Wochenschrift, Berlin

21:145-168 (Feb. 14) 1942. **Partial Index**

*Action of Immune Serums in Bacteriotoxic Inflammation. G. Säker.—p. 145.
Effect of Gonadotropic Substance After Roentgen Therapy on Regeneration of Testis in Rats. H. von Wattenwyl.—p. 148.
Importance of Erosion in Pathogenesis of Carcinoma of Pavement Epithelium of Cervix Uteri. H. Hinselmann.—p. 152.
*Clinical Aspects of Typhoid. W. von Drigalski and H. Martin.—p. 158.
Experimental Demonstration of Resorption of Desoxycorticosterone and Desoxycorticosterone Acetate in Percutaneous or Peroral Administration. W. Hohlweg.—p. 160.
Thymotropic Hormone of Anterior Lobe of Hypophysis and Thymus Hormone: Remarks on Paper by Anselmino and Lotz. C. Bomskov.—p. 162.

Immune Serums in Bacteriotoxic Inflammations.—Säker found that intrathecal injection of cerebrospinal fluid from purulent cases of meningitis produces a severe inflammation of the arachnoid. Normal cerebrospinal fluid from sterile cases of meningitis does not cause any meningeal inflammation. He concludes that the infectious inflammation is caused quantitatively by certain inflammatory toxins of the bacteria and that these bacterial products originate in the area of infection and result in an inflammatory reaction. The intensity of inflammation depends directly on the quantity, the virulence and the production of toxins by the type of bacteria concerned in the focus of infection. Thus the degree of infection is in simple proportion to the bacteriotoxic damage of the tissues. The effect of an immune serum on the inflammatory toxin of the cerebrospinal fluid used in experiments was observed in intrathecal injection of a mixture of both these substances after an incubation period of two days. The action of the serum was investigated likewise in vivo. The commercial immune serums did not exert any action either in vitro or in vivo on the bacteriotoxic inflammation. No unspecific serum effect on the reactive tissue inflammation could be observed. The tissues did not become accustomed to and no "active immunity" of the tissues against the inflammation toxins was produced by the toxins themselves or by specific vaccine. Thus the inflammation toxins should be considered as simple cellular poisons without the antigen property, and serum therapy cannot be considered effective for passive protection against infection from bacteriotoxic inflammation.

Symptoms of Typhoid.—Von Drigalski and Martin state that there is no one symptom present in all of the cases of typhoid. The temperature curve and eosinopenia are the most trustworthy. Leukopenia and the Gruber-Widal reaction are positive in about three fourths of all cases. Bacilli were demonstrated in feces and urine of about two thirds of the cases. Roseola was next in frequency, followed by enlargement of the spleen, Ehrlich's diazo reaction and bradycardia. Generalized enlargement of the lymph nodes, initial neuritis in the area of the left brachial plexus and pronounced splenomegaly in the absence of almost all important symptoms of typhoid were observed in individual cases. The clinical picture of typhoid may be atypical because of the absence of classic symptoms and because of the presence of unusual symptoms. It may present a picture entirely different from that given in textbooks.

Wiener klinische Wochenschrift, Vienna

55:161-180 (Feb. 27) 1942. **Partial Index**

Circulation and Metabolism. O. Müller.—p. 161.
Hereditary Pathology and Sterilization Law. M. Gundel.—p. 168.
*Increase in Perforation of Peptic Ulcer in Wartime. A. Slany.—p. 171.
Can Desire of Practitioner for Unified Formula for Infants Be Fulfilled? A. von Reuss.—p. 172.

Increase in Perforation of Peptic Ulcer in Wartime.—Surgical intervention for perforating peptic ulcer was performed at the General Hospital of Wiener Neustadt in from 3 to 4 cases per month after the outbreak of the war as contrasted with 1 to 2 operations in peacetime. Instances of perforation of peptic ulcer were nearly doubled. They were acute in the majority of the cases and occurred exclusively in men. Change of living habits resulting from wartime production, change from day to night shifts and vice versa, irregular and cold meals, close attention to work, and excitement caused by war affect the vegetative system. Perforations occurred predominantly in heavy smokers. Nicotine by its effect on the vegetative system may be of foremost importance in the pathogenesis of peptic ulcer.

Book Notices

Psychosomatic Medicine: The Clinical Application of Psychopathology to General Medical Problems. By Edward Weiss, M.D., Professor of Clinical Medicine, Temple University Medical School, Philadelphia, and O. Spurgeon English, M.D., Professor of Psychiatry, Temple University Medical School. Cloth. Price, $8. Pp. 687, with illustrations. Philadelphia & London: W. B. Saunders Company, 1943.

For the first time the subject of psychosomatic medicine has been brought before the medical profession in a clear, concise and informative discussion. The opening chapter gives the reader a concept of the problem. As the authors aptly point out in the summary "The study and treatment of illness constitutes much more than the investigation and eradication of disease." The chapter on personality development and psychopathology is exceedingly well handled and instructive. From there on the authors take up the various systems of the body in relation to the emotional disturbances and the end results of hyperfunction and hypofunction. These manifestations are presented from the point of view of case history along with suitable discussions. The treatment is handled in a very composite manner. The book as a whole serves an important need of the medical profession and it should be of particular interest to teachers in medical schools, who must become thoroughly familiar and imbued with the importance of psychosomatic medicine. Therefore it is highly recommended as one of the important contributions to the medical literature of the year.

Clinical Significance of the Blood in Tuberculosis. By Guill Lindh Muller, M.D., Pathologist and Director of Laboratory, New England Hospital for Women and Children, Boston. Cloth. Price, $3.50. Pp. 516, with 19 illustrations. New York: Commonwealth Fund; London: Oxford University Press, 1943.

This book, on the clinical significance of the blood in tuberculosis, is more than a mere description and tabulation of the various hematologic manifestations of the disease. In fact, it often goes rather far afield in the discussions relating to such features as the sedimentation rate and the various hematologic indexes. However, this is by no means a disadvantage, since one may obtain in this book an exceedingly well documented and complete description, including historical summaries, of the Arneth count, the Schilling hemogram and the monocyte-lymphocyte ratio. Since good descriptions of these subjects are often obtainable only in scattered form elsewhere, this is very helpful to the interested student.

Excellent descriptions of the bone marrow, the various cellular reactions to disease, the monocyte and other subjects are presented, together with well balanced commentaries on the various indexes which have been offered as short cuts to the diagnosis and prognosis of tuberculosis. The attempts of Sabin, Doan and Cunningham to elevate the monocyte, supravital staining, and the monocyte-lymphocyte ratio to high standing are thoroughly investigated, the conclusion being made that an "increase, decrease or lack of change in the number of monocytes per se . . . gives but little indication of the state of the tuberculous process." The status of the lymphocyte offers a somewhat better indication, since these cells become increased with healing and vice versa. Supravital preparations—and this is the reviewer's experience as well—have been greatly overrated. They are furthermore stated to be time consuming, not permanent, and limited as to time of observation.

All the numerous hematologic "tricks" which have been proposed for the study of tuberculous blood are thoroughly and wisely discussed, such as eosinophilia, absolute vs. relative numbers of leukocytes, study of immature polymorphonuclears, toxic changes and the reaction of the blood to tuberculin. In addition the anemia, the leukemoid reactions which occasionally occur especially in miliary tuberculosis and hemorrhagic manifestations are discussed. The reviewer hastens to reemphasize Dr. Muller's statement that little (I would say nothing) can be gained by the use of expensive liver extracts in the treatment of the anemia of the disease. If this product should be used only for pernicious anemia, which is really the sole disease in which liver extract is indicated, imagine how sharply the sales of the product would be curtailed.

A large section of the book is devoted to the sedimentation rate, fifty-five pages in all being given over to a general discussion of this important test. The numerous technics are adequately described and criticized, and a new correction table is presented. Unfortunately there is no general discussion of the value of the test in various phases of the disease. One also misses at the end of the book a general, over-all view of the value or lack of value of the various tests. In other words, the details are beautifully painted in, but there is lacking a general integration of the whole picture with the result that the reader does not get a unified conception of the author's conclusions. However, of the various hematologic components listed—increased sedimentation rate, neutrophilia, shift to the left, monocytosis, lymphopenia and lymphocytosis, eosinopenia and eosinophilia—the most important to watch from a prognostic standpoint are the sedimentation rate, the shift to the left and the lymphocyte percentage.

The book is well written and printed. The studious and exhaustive nature of the monograph is attested by the excellent bibliography, which contains six hundred and four complete references.

A Family of Thirty Million: The Story of the Metropolitan Life Insurance Company. By Louis I. Dublin, M.D., Third Vice-President and Statistician, Metropolitan Life Insurance Company. Cloth. Pp. 496, with illustrations. New York: Metropolitan Life Insurance Company, 1943.

This is the history of the Metropolitan Life Insurance Company, but it is more than that. It is also the history of insurance and its growth with the growth of the nation, its troubles and trials, its shortcomings and its triumphs, and, most of all, its contributions to the nation's financial stability, social development and public health. The author writes exhaustively of the growth and development of the Metropolitan but deals generously also with other companies competing in the same fields. The book reflects more than mere pride in financial success, though there is plenty of that, for the Metropolitan is not only the world's largest insurance organization but the world's largest financial corporation. Through the book shines the spirit of the men who made Metropolitan great because they were more than shrewd businessmen and canny financiers. They were that, but they were men of broad vision too, who saw that nothing makes a man or an organization great more surely than to be of service to other men. The history of Metropolitan, as set forth in this book, could be summed up in one simple statement—it has consistently given more than it was compelled by contract to give to its policyholders and to the nation. This is manifested in repeated liberalization of contracts, often retroactive, in generous treatment of lapsed and reinstating policyholders, in prompt handling of claims and in a general attitude of liberality toward all proper claims.

Of special interest to physicians is the chapter on relationships to medical science and public health, in which fields the Metropolitan has contributed generously through grants for research and demonstration, and participation in numerous projects. The Welfare Division, making nursing services available to its millions of industrial, group and intermediate policyholders, and contributing billions of free pamphlets to health education, as well as numerous exhibits, loan films and a help by correspondence service for school teachers, is typical of the spirit of service which has been evident throughout the history of the Metropolitan. That this has been profitable in no way detracts from its significance; since the mutualization of the company, voluntarily carried through by its stockholders, the benefits of profitable operation have accrued to all the policyholders.

The book itself, aside from the history of a great institution which it portrays, is interesting. Dealing with numerous figures, many personalities out of the past and numerous matters which might easily have become dull, it nevertheless contrives to be interesting throughout and sometimes exciting. Every chapter, every paragraph, hews to the line, telling a story of service. That the author has been a part of much of this history, has rubbed shoulders with those who have made and are making it and has made some of it himself—the Statistical Department and its valuable publications, notably the *Statistical Bulletin*, which is said to have more readers than any best seller—enables him to write with authority and enthusiasm.

The book is also a mine of information about insurance in terms which the inexperienced reader can readily understand.

It is, in addition, an important social document. It offers the institution of life insurance and collateral lines such as accident, health, hospital expense and surgical expense insurance as America's answer to the problem of social security. It demonstrates how even the poor man, through industrial or group insurance, can provide means to keep him off the relief roll and to maintain his self reliance and self respect. This philosophy is perhaps best stated in the words of the preface: "At this time in our history, when the desire for security is greater than ever before, it is hoped that this volume will reflect what the American people have done through life insurance to provide financial protection for themselves. They have achieved this security to a greater degree than any other people, achieved it voluntarily, and through institutions of their own making. This is an American tradition. They have not depended upon government subsidy but have themselves taken the initiative. Americans apparently prefer this method, which takes into account individual needs and relies on the sense of obligation of the head of the family to look after his own."

Kitchen Strategy: Vitamin Value Made Easy. By Leona M. Bayer, M.D., Assistant Clinical Professor of Medicine, Stanford University School of Medicine, San Francisco, and Edith S. Green, B.A. Paper. Price, $1.50. Pp. 107, with illustrations by Antonio Sotomayor. San Francisco: The Authors, 1943.

This is a ring binder looseleaf booklet dealing with the practical aspects of choosing, buying, preparing and cooking foods that will supply the essentials of good nutrition and still make the family think they are just eating food—a consummation devoutly to be wished in these diet conscious days. It is attractively embellished with cartoons. The section on menus for common ailments should either have been omitted or have been amplified. In the hands of the lay person, for whom this booklet is obviously intended, this section might suggest that these are the only menus, whereas they are samples. The author explains this, but the criticism holds nonetheless. There are excellent chapters on substituting more common for scarcer foods; these should prove invaluable if rationing really grows severe. All in all, the book may be recommended, with the possible exception of pages 33 to 41, for the reasons set forth.

Medical Biochemistry. By Mark R. Everett, Ph.D., Professor of Biochemistry, University of Oklahoma School of Medicine, Oklahoma City. Medical Students' Series, edited by Fred C. Zapffe, Secretary, Association of American Medical Colleges, Chicago. Cloth. Price, $5.75. Pp. 694. New York & London: Paul B. Hoeber, Inc., 1942.

This book, which is one of several in the Medical Students' Series, is intended to present "a modern, concise and correlated survey of biochemical knowledge for students of medicine and allied subjects." It is supposed to be part of "a new approach to textbook writing," as is envisaged in the Medical Students' Series, books written specially for students rather than for academic didactics alone. The contents include discussions of acid-base relations, colloids, enzymes and oxidation, digestion, lipids, carbohydrates, proteins, prosthetic radicals of nucleoproteins and chromoproteins, inorganic substances, vitamins and avitaminoses, hormones and endocrinoses. An addendum offers a guide to biochemical literature. There are two indexes, a general index and an index to tables; both are quite complete and useful.

The editor of this series, Fred C. Zapffe, states "So much time, thought and effort have been put into this project that it should warrant a fair trial by all those who are competent to pass judgment—teachers and students in the fields covered." The preparation of books intended primarily for students is commendable; often there are too few textbooks with this objective in a given field. Sometimes, however, such textbooks present material which is best left for other sources; medical biochemistry is one of these. It presents many excellent digests on biochemical questions but occasionally borders too closely on problems such as avitaminoses and endocrinoses, which are best left to other special treatises. There is no denying that a knowledge of the chemistry of the body functionings is as essential as a knowledge of the pathologic changes and accepted treatments; otherwise it would be difficult to understand and treat properly many diseases, especially those due to deficiencies. However, if this book is "to offer the medical student a volume which presents the basis of the subject in such form and degree of detail as he can absorb in the time allotted," the contents should be reserved for biochemical considerations with only sufficient reference to diseases and pathology to orient the student with the reasons for teaching and learning such subjects as biochemistry. Apart from this criticism, the book, if used as a book of this nature should be used, is one that can be useful for the teacher and student. It is easy to read and has a sufficient but not depressing number of formulas and tables to make clear most of the author's statements.

Cancer Control: The What, Whither, How. Edited by Channing C. Simmons. Paper. Price, 50 cents. Pp. 86. Boston: Massachusetts Department of Public Health, Division of Adult Hygiene, 1943.

This is a publication of the Massachusetts Department of Public Health in close collaboration with the state medical society. It deals with the cancer control program in the state, with special attention to health education and its possible contribution to the solution of the cancer problem. The committee seems either to be at a loss what to say about health education and cancer control or unwilling to say what it thinks. Part III of the report, dealing with how cancer education should be conducted, "has not been written. It is hoped that several . . . committees will devise outstanding educational methods which will warrant being included in this section. . . ." Other chapters deal with cancer prevention as far as preventive measures are known, with methods of treatment and with research. This eminently erudite and dignified publication will have a small circle of interested—previously interested—readers but will not do much to bring knowledge of cancer to the man in the market place or his wife in the home or the factory—which is where cancer education has to go. It has to go there in much less dignified garb and in much plainer, easier, simpler, more understandable terms—and much briefer.

Biological Symposia: A Series of Volumes Devoted to Current Symposia in the Field of Biology. Edited by Jaques Cattell, Editor of the American Naturalist and American Men of Science. Volume IX: Sex Hormones. Edited by F. C. Koch, Frank P. Hixon Distinguished Service Professor and Chairman of the Department of Biochemistry of the University of Chicago, and Philip E. Smith, Professor, College of Physicians and Surgeons, Columbia University, New York. Cloth. Price, $2.50. Pp. 146, with illustrations. Lancaster, Pennsylvania: Jaques Cattell Press, 1942.

This book is the ninth in a series of volumes devoted to current symposiums in the field of biology. Edited by men renowned in the respective fields, the series is one that should be available in all reference libraries. The present volume, which includes the papers from the symposium on sex hormones presented at the fiftieth anniversary celebration of the University of Chicago in September 1941 and the symposium on hormonal factors in sex inversion presented at the annual meeting of the American Association of Anatomists in April 1942, adds to the credit of the series. The contents include discussions of the comparative biology of testicular and ovarian hormones by C. R. Moore, the comparative metabolic influences of the testicular and ovarian hormones by A. T. Kenyon, the metabolism of estrogens by E. A. Doisy, the excretion and metabolism of male sex hormones in health and disease by F. C. Koch, sex inversion in the plumage of birds by C. H. Danforth, sex inversion in the amphibia by R. R. Humphrey, the effects of sex hormones on embryonic sexual structures of the rat by R. R. Greene and hormones and experimental modification of sex in the opposum by R. K. Burns Jr. While the presentations are as general as would be expected in such symposiums, most of them can be read with interest and profit not only by the specialist in this field but by others if they possess even a spark of interest in endocrinology.

Nursing History in Brief. By Minnie Goodnow, R.N. Second edition. Cloth. Price, $2.25. Pp. 338, with 103 illustrations. Philadelphia & London: W. B. Saunders Company, 1943.

This is designed as a textbook for short courses in nursing history (fifteen hours or less). It is well organized, clearly and interestingly presented and well illustrated. It begins with the story of nursing efforts among primitive peoples and includes material as recent as the nursing records of the current war. A general historical chronology and a chronology of nursing history are given. Review questions are presented at the end of the book, not chapter by chapter. There is an excellent index.

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Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

SKIN PEELING FOR ACNE

To the Editor:—A young girl has severe acne which has resisted all routine therapy. A course of x-ray treatment left deep pitting of the lesions. The family has asked my advice concerning skin peeling. I intend to start with 3 per cent sulfur and salicylic acid, beginning with a small area. I have a good idea of the technic, but kindly inform me of the exact procedure and if there is any better medication than the one I have mentioned. George H. Jantzen, M.D., Queens Village, N. Y.

To the Editor:—A young girl in my practice has had serious scarring of her face from acne. She has had x-ray treatment, and deep red scars are present. The question arises as to whether her face should be peeled after school is over. Would you please advise me as to what benefit might be expected from peeling her face after having gone through with x-ray treatment of her skin? Hubert B. Haywood, M.D., Raleigh, N. C.

ANSWER.—Skin peeling is not used as generally in this country as in Europe because of the dangers. When done carefully it gives satisfactory results. The chief dangers include production of an acute dermatitis in a skin sensitized to one of the drugs used, of an overeffect, causing a chronic erythema or even necrosis of the skin and of absorption of the drug resorcinol or betanaphthol, harming the kidneys. These may be guarded against by preliminary patch tests, by a cautious approach and by careful and repeated examination of the urine.

Brocq's formula for a keratolytic salve for severe acne of the trunk is as follows:

	Gm. or Cc.
Resorcinol	
Camphor ..... āā	10.00
Potash soap	15.00
Precipitated sulfur	30.00
Prepared chalk	5.00
Petrolatum	30.00

Formulas for other mixtures may be found in A Text Book of Dermatology, by J. Darier (authorized translation of the second French edition, edited with notes by S. Pollitzer, Philadelphia and New York, Lea & Febiger, 1920, p. 732).

A good description of the technic is given by Kren (Kosmetische Winke, Vienna and Berlin, J. Springer, 1930, p. 25). He refuses to attempt this treatment for any one with impaired kidneys and insists on a careful urinalysis before each application of the exfoliating paste, which is composed of:

	Gm. or Cc.
Betanaphthol	10.00
Flowers of sulfur	40.00
Green soap	
Petrolatum ..... āā	25.00

If the yellow mass turns brown because of the effect of light on the betanaphthol, no harm is done. Only part of the face should be treated at a time: cheeks and chin, for instance, the first time, nose and forehead at a later time. The part to be treated is first washed with benzine to remove fat, and then the paste is applied about 2 mm. thick. The clothing must be protected, since the paste causes spots. A moderate burning sensation is experienced, but it lasts only a few minutes. After the paste has remained for from twenty to thirty minutes it is removed with dry cotton or fine gauze, care being taken to remove it all. No water or soap is allowed. The skin will be slightly reddened, but this clears in a few hours.

On the next day, or even after twelve hours, the process is repeated and each day again until slight exfoliation begins. The urine should be examined repeatedly to guard against kidney irritation. If albumin or casts appear, the treatment must be given up.

One per cent salicylic acid in alcohol, applied night and morning, is the only washing this part of the skin is allowed. After peeling begins, this solution is to be dabbed on several times a day. After about five days' use of the exfoliating paste, the process will be complete in three or four days. Left on the skin too long, the paste may cause ulceration. The whole procedure, applied to the whole face in two separate treatments, takes a little more than two weeks.

A milder, more easily controlled procedure has been used for a number of years for the same purpose, with excellent results in many cases. This is the application of a slush of solidified carbon dioxide and acetone. Recently sulfur has been added. Karp, Nieman and Lerner (Cryotherapy for Acne and Its Scars, *Arch. Dermat. & Syph.* **39**:995 [June] 1939) describe the technic as follows:

"The apparatus consists of a large clay mortar and pestle, solid carbon dioxide, acetone, precipitated sulfur, absorbent cotton, a square of gauze and a wooden tongue depressor. Approximately 5 ounces (140 Gm.) of solid carbon dioxide is placed in a large clay mortar and ground to a fine powder. Acetone (dimethylketone) is carefully added with constant stirring until a smooth paste is obtained. Then with a wooden spatula approximately ¼ ounce of precipitated sulfur is added until a light yellow mixture is formed. If necessary a few additional drops of acetone may be added.

"About one third of the paste is placed on a tampon of absorbent cotton, covered with a square of gauze, and applied under moderate pressure to the most prominent lesions. The tampon is then immersed a second time in the paste. At this stage the addition of a small amount of acetone is usually necessary. The carbon dioxide paste is now applied directly to the skin. The application is made without pressure, and the entire face is covered with rapid friction. The resulting deposit of sulfur is allowed to remain on the face for approximately twenty minutes after the treatment. Immediately after application, erythema and slight edema appear, which last about two or three days and are followed by mild exfoliation of the epidermis. Applications are repeated at weekly intervals. Note: Acetone is inflammable." They report excellent results but warn against the danger of using it on atrophic skin or on melanomas. Even when roentgen treatment has been mild, it adds to the risk of excessive reaction to the cryotherapy. They believe that the improvement of scars is due to the lessening of their sharp outline and increase of circulation and skin tone.

Dobes and Keil (Treatment of Acne Vulgaris by Cryotherapy [Slush Method], *ibid.* **42**:547 [Oct.] 1940), applying it generally, had good results in 16 of their 69 papulopustular cases; but by applying it locally to individual nodules in the cystic cases they cleared up a much larger proportion. They encountered some difficulties. Among their patients were two with cold allergy, who responded to the treatment with immediate urticaria and a burning sensation lasting several hours. Another patient reacted to cold, even cold weather, with a new crop of pustules. A severe edema of the face occurred in 1 girl and lasted two days. A Negress developed a patch of depigmentation lasting for months. Deeply tanned white persons showed no such result. From a trial application of the slush 1 patient developed a blotchy purpuric erythema ending after a month in mixed hyperpigmentation and hypopigmentation. Thus the method has a limited field, taking the place of the old peeling methods because of its deeper action and greater ease of control. Dobes and Keil are not much impressed with the improvement of scars. They quote Karp's opinion that at least eight months of treatment is needed to show decided improvement of acne scars, while those resulting from smallpox should be given seventy-five to eighty treatments. They omit the sulfur from the slush for the treatment of scars.

So far no one has devised an objective method of measuring the results of treatment of multiple small scars such as those occurring as a consequence of acne. There is no doubt, however, that the impression that the scars are less noticeable, in spite of the skepticism of the physician, has a beneficial effect on many patients. Karp, Nieman and Lerner warn against the too energetic treatment of scars. Repeated mild treatments give the best results, and time must be allowed for the effects of one treatment to subside before repeating it. These rules should apply also to the chemical peeling process.

PROBABLE ALOPECIA AREATA OF BEARDED AREAS

To the Editor:—A man aged 50 has an area of alopecia on each side of the cheek. The duration is about two years and the areas are gradually increasing in size, localized to these two spots. The physical examination is essentially negative. Previous physicians consulted had informed the patient that there is no treatment effective. I shall appreciate advice as to investigation and treatment. Esther Tuttle, M.D., New York.

ANSWER.—The inquirer does not give any details about the patches of alopecia. It is assumed that there has been neither scar formation nor atrophy produced and that there is no visible inflammation present. Without the presence of inflammation, one can discard such possibilities as ringworm infection of the beard and coccogenous sycosis. Tertiary syphilis, lupus erythematosus and favus can be ruled out because there is no scarring or atrophy. The probable diagnosis, therefore, is alopecia areata.

Alopecia areata is rather common on the scalp but appears less frequently at other sites. The bearded area, however, is

not rarely involved. The characteristics of the disease here are no different in any essentials from those on the scalp. The hair falls to leave a clean, noninflamed patch or patches and there is no progression to scar formation. The borders of the patches are fairly well defined and regular. In an actively forming area there may be found the well known "exclamation point" hairs showing narrowing at the base. One would not expect to find such hairs at the edges of patches of two years' duration.

Alopecia areata seems to take a course which often extends from several months to two years with extremes in some of much shorter and longer duration. Thus one must be careful not to draw unwarranted conclusion from the results following any special regimen in a particular case. In general the outlook for any patient depends on the extent of the alopecia and the age of the patient. Younger ones do better, so that a middle aged person such as the one under consideration would not be expected to do well. Those who get well have regrowth of hair in any one patch relatively early, though prolongation of the process takes place by new patches forming. In a middle aged man who has the same areas present without regrowth and with spreading of their borders the prognosis is bad. If there are any hairs present even to the finest lanugo, it is worth treating the patient. It is possible that this effort may help to stay the progress of the disease.

The entire patient should receive attention. Many believe that alopecia areata is mediated by mental stress or through nervous reflexes. This should be explained to the subject to gain his cooperation in the attempt to resolve worries and irritations. He may need rest and reduced responsibilities. Sources for reflex stimuli such as infections of sinuses or teeth should be hunted and eradicated. Anemia or indications for tonics may be present. Some observers laud hydrotherapy. Local measures include the application of materials to stimulate the sites of alopecia. A popular one is the painting with liquefied phenol. This produces a whitish parboiled appearance, at which time alcohol is quickly applied to neutralize the phenol. Recovery from the induced inflammation takes place in five days or a week, when the applications are remade. These reapplications may be given over a prolonged period. Cutler's fluid may be used instead of phenol. Cutler's fluid consists of equal parts of liquefied phenol, tincture of iodine and chloral hydrate. Numerous other applications of similar character are recommended, but these probably have no greater merit. Ultraviolet ray applications are useful and popular. Frequent shaving makes the patches over the beard less conspicuous.

THROMBOSIS OF SAPHENOUS VEIN AFTER HYSTERECTOMY

To the Editor:—A hysterectomy was performed on March 24, 1943 on a woman who is 45 years of age. She developed phlebitis in her right internal saphenous vein. She had a slight elevation of temperature and palpable beating of that vein. The temperature subsided in about three days, and at present there is little tenderness along the saphenous vein, but she has a great deal of tenderness in the calf region of her leg. I treated her conservatively and we have a difference of opinion as to whether she is a proper subject for injection of procaine hydrochloride into the lumbar region on that side. Kindly advise me what is considered the best treatment for this condition today. M.D., Connecticut.

Answer.—It is impossible to give a categorical answer to this query, since it is uncertain from the description as to what type of thrombosis developed after hysterectomy. Postoperative thrombosis affecting the saphenous vein alone is infrequent unless there are preexisting varicosities of the saphenous vein. If this should be the case, a ligation of the saphenous vein and its tributaries at the saphenous femoral junction is the method of choice. The pain in the calf demands the consideration of the possibility that the muscle veins of the calf may also be involved. This type of thrombosis often extends to the deep veins of the lower leg and may be the source of embolism. A slight cyanosis in the dependent position and pain in the calf or popliteal fossa on dorsiflexion of the foot are further suggestive findings of deep venous thrombosis of the lower leg. If facilities are available a radiopaque solution may be injected into a small superficial vein on the foot and the patency of the deep veins visualized. If a diagnosis of deep venous thrombosis of the lower leg can be made, the best current opinion is that a ligation of the femoral vein below the profunda is indicated since it prevents embolism. This is especially true of patients close to 50 years of age, since the incidence of embolism rises after the fifth decade. If prothrombin determinations can be made, the extract of spoiled sweet clover (dicumarol) can be cautiously administered to offset the increased clotting tendency of the blood and prevent further spread of thrombosis.

The procaine hydrochloride injection of the lumbar sympathetic chain relieves the pain and the acute edema of a deep thrombosis. It is most useful in the first few days after the onset and seems less and less useful after the early pain and edema have subsided. Its purpose is to inhibit a vasospasm of the small arterioles and venules, which is due to an autonomic reflex originating in the thrombosed vessel. If the thrombosis is chronic, if there is no pain and edema, the nerve block is unnecessary.

TREATMENT OF FRACTURES ABOUT ELBOW

To the Editor:—I was taught to put up fractures around the elbow in the "Jones position": the arm acutely flexed, the thumb and fingers grasping the throat. This method, it seems to me, has objections. The blood cannot be used, and the amount of dressings required is considerable and somewhat difficult to apply and to keep in place. In the summer months such a dressing is hot and causes free perspiration followed by irritation of the skin, as well as some bad odor. The shoulder and hand cannot be exercised. In a small town I do not have the opportunity to see many injured elbows. However, I have recently seen a severe injury to the elbow in a 9 year old girl. I put her arm up according to my own ideas, and I got a perfect result—no deformity and complete restoration of function. Whether the method is old and I just haven't heard about it or seen it described in the textbooks, I don't know. The method is simplicity itself. I flexed her arm just as I would have done in the Jones method. I held it in this flexed position by passing an adhesive strip in such a way as to go round the forearm just below the wrist and the upper arm just below the axilla. I put a small piece of cotton in the fold of the elbow—and that was all there was to it. The patient could exercise her fingers and shoulder, could even use her hand for some things. The skin is easily reached for cleansing purposes, the dressing is easily and quickly applied and is a minimum of trouble to change. Free ventilation is allowed between the arm and the body. If this method is wrong, I should like to know it. If it is right and has not already been described, I should like others to know about it.

Emory R. Park, M.D., La Grange, Ga.

Answer.—The "Jones position" of the forearm flexed directly over the arm as the axes of the two coincide is orthodox and widely used. It does not effect or maintain reduction of all types of fractures about the elbow. It is described in textbooks. The reduction procedure for supracondylar fractures of the humerus, mostly in adolescents, is slight extension of the forearm during traction on it, followed by flexion into position with axes superimposed. No effort is made to have the fingers clutch the throat, as that may cause rotation of the forearm and result in incomplete reduction. The reduction is checked by x-ray examination in two planes, anteroposterior and lateral, through the elbow. (See Primer on Fractures.) This position may be maintained by a posterior molded plaster splint from the upper arm to the base of the fingers, which leaves the shoulder free for motion and the arm for abduction. If the wrist is allowed too free motion it may cause displacement of the fragments of the humerus by rotation of the forearm. The arm, thus splinted, may be carried in a sling and need not cause skin irritation from sweating, as the whole arm can be lifted and held up in abduction without disturbing the reduction at the elbow. It is possible, in the small arm of a child, to hold this position with adhesive tape with a small sterile pad in the antecubital space, but the heavier arm of an adult may slip out of the adhesive or by its weight cause skin irritation. The method described in the query was perfectly adequate. It is not new and was popularized by Ashhurst thirty years ago. After any of these dressings, it must be known that the circulation (radial pulse) remains normal in the limb.

ACROCYANOSIS AND AUTOAGGLUTINATION OF RED CELLS

To the Editor:—A case of clinical acrocyanosis recently came into our hospital. When a routine venipuncture was performed for blood studies it was noted that the blood clotted so quickly that examination of the blood was impossible. When blood was drawn into ordinary red blood cell and white blood cell pipets the same phenomenon occurred in the chamber of these pipets. Microscopic examination of these clumps of cells revealed that the red blood cells were massed together either in rouleaux formation or simply massed together in nonrouleaux formation. No fibrin was present. Heating the chamber of a pipet containing these clumps of red blood cells resulted in the disintegration of the clumps, and microscopic examination then revealed perfectly normal appearing erythrocytes and leukocytes. The red blood cell and white blood cell counts were normal. In examining the literature I have found no definite statement of the cause of acrocyanosis. I should appreciate information from you as to what is now considered the most likely explanation of acrocyanosis and whether the herein described phenomenon has ever been described in association with acrocyanosis. Lieutenant, M. C., A. U. S.

Answer.—Autoagglutination or "cold" agglutination of red blood cells has been observed in a number of persons (Walther, G.: *Folia haemat.* **38**:281 [July] 1929). McCombs and McElroy: *Arch. Int. Med.* **59**:107 [Jan.] 1937) reported a case in which autoagglutination was associated with acrocyanosis

and cited 5 additional cases from the literature. Two of the authors advanced the hypothesis of autoagglutination as a cause of Raynaud's disease. Two more cases were reported by Benians and Feasby (Raynaud's Syndrome with Spontaneous Cold Hemagglutination, *Lancet* **2**:479 [Oct. 25] 1941). Autoagglutination in a patient with acquired hemolytic anemia has been observed. On exposure to cold, the face and hands become definitely cyanotic.

It is apparent that acrocyanosis, which is usually considered to be due to vasospasm, may also be related to autoagglutination.

PENILE ULCERS

To the *Editor*:—In a genitourinary clinic and genitourinary ward recently smears in 4 cases of extraurethral lesions were positive for gram negative diplococci. One patient had two small abscesses of the shaft of the penis and smears were repeatedly positive for gram negative diplococci. No history of previous gonorrhea or recent urethral discharge could be obtained. Cultures were oxidase positive. The second patient had small penile ulcers with repeated negative dark fields. Smears stained with Gram's stain showed gram negative intracellular diplococci, culture from lesions gave positive oxidase and transplants to sugar mediums were positive for Neisseria gonorrheae. The third and fourth patients had penile ulcers, from which smears showed extracellular gram negative diplococci. Cultures and further studies are being made. I am interested in opinions as to the possible causation of these acute penile ulcers. In all cases the lesions appeared from four to ten days after intercourse and this incubation period, plus the data heretofore mentioned, makes me feel that the gonococcus is the causative agent of many penile lesions previously classified as "cause undetermined."

Captain, M. C., A. U. S.

ANSWER.—Several cases similar to these have been reported in the British literature in which it was thought that the penile ulcers were due to Neisseria gonorrheae. However, since gram positive cocci in certain lesions appear gram negative and even intracellular in gram stained smears, it would appear that the lesions described may not be caused by N. gonorrheae. The positive oxydase reaction is also given by some types of micrococci and other bacteria. Small gram negative diplococci or coccobacilli formerly called Gurd's diplobacillus are occasionally found in eroded areas in the female vagina and can infect abraded areas on the shaft of the penis. One should subject the cultures of cocci to all determinative criteria before actually describing the condition as extraurethral gonococcic ulcers.

INTRAVENOUS INJECTION OF AIR

To the *Editor*:—I should like to establish whether the blood stream of the average human being can absorb 1 cc. of air which is injected into it under 30 pounds of pressure. This question arises from certain inquiries about a new development project and it would be most desirable if an answer could be secured as soon as possible.

Clark D. Bridges, Industrial Hygienist, Chicago.

ANSWER.—The effects of the injection of 1 cc. of air under 30 pounds pressure into the blood stream of the human being would obviously vary with the site of injection. Injection into one of the systemic veins would probably not give rise to serious consequences, since the oxygen would be taken up mainly by the hemoglobin and slightly by simple solution in the venous blood and the nitrogen would be filtered out by the pulmonary capillaries. However, rarely one or more bubbles of nitrogen will pass through the pulmonary circulation to the left heart chamber and if a nitrogen embolus should lodge in one of the coronary arteries or one of the arteries supplying the vital medullary centers the consequences would be serious or even fatal. Usually, however, much larger quantities of air intravenously are required to produce death by air embolism. Injection of the air into the left heart chamber would certainly afford good opportunity for coronary embolism and fair opportunity for medullary embolism. Likewise injection into one of the main carotid arteries would likewise entail definite risk of medullary embolism. Injection of the air into other systemic arteries would involve less risk. Obviously 1 cc. of air under a pressure of 30 pounds would expand to approximately 3 cc. when introduced into a vein and to only slightly less than 3 cc. if injected into an artery. The injection of the air under the pressure mentioned might lead to rupture of the vein or even the artery at the site of the injection, although this would be unlikely. The absorption or solution of the nitrogen would be slow under normal circumstances, although previous denitrogenation of the human subject by the breathing of pure oxygen would, of course, permit rapid solution of the nitrogen in the blood and tissues.

INHERITANCE OF PSEUDOHYPERTROPHIC FORM OF MUSCULAR DYSTROPHY

To the *Editor*:—A healthy white woman is gravid for the first time since her first pregnancy twelve years ago. Her first born son has a pseudohypertrophic form of muscular dystrophy. She fears that this offspring may be afflicted with the same condition. What is known about the hereditary aspect of this disease? What should one advise this patient about continuing her pregnancy?

M.D., Virginia.

ANSWER.—The pseudohypertrophic form of muscular dystrophy is considered a hereditary disease. When it appears in successive generations in a family, it has mendelian dominant characteristics. In this type of inheritance the chances of it appearing in sibship is almost 50 per cent, the sexes usually being affected with equal frequency. If, on the other hand, the disease has not occurred in previous generations and thus may be looked on as a recessive factor, the chances of inheritance are less. In spasmodic cases of this type the disease is more prevalent in the male in a frequency of about three to one. In order, therefore, to estimate whether a second child would have pseudohypertrophic muscular dystrophy, when the first child was so afflicted the history of the disease in previous generations should be obtained. Advice with regard to continuance of the pregnancy cannot be given in a categorical manner. The facts, however, as known may be placed before the family.

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Barnes, Stanley: A Myopathic Family, *Brain* **55**:1 (March) 1932.
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DIAGNOSIS OF RECURRENT SKIN LESIONS IN WINTER

To the *Editor*:—A man aged 51 states that twenty-five years ago following exposure to cold he sustained a severe case of frostbite involving the hands, forearms and both earlobes. Since that time, starting in late September and extending to early May, a dermatitis involving the hands, forearms and earlobes makes its appearance. The skin hardens, cracks easily and is reddened, and there are scattered papular lesions. Glycerin applied to the exposed parts appears to offer systemic relief, although it does not cause the skin lesions to disappear. Various possibilities such as occupational dermatitis, soap dermatitis and water dermatitis were considered. He has changed his occupation and at present is a supervisor and does not do manual labor. He does use a castile soap and avoids wetting his hands as much as is consistent with body cleanliness. The blood serologic reaction, sedimentation rate, platelet count, cell count and renal function tests are negative. Could you describe the physiologic basis for the disorder described and also plan a course of therapy? Is there merit to the therapy of ionization, using salicylic acid, histidine or sodium chloride as an electrolytic base?

Charles S. Mirkin, M.D., New York.

ANSWER.—The possibility of a seasonally recurring dermatitis venenata or contact dermatitis has been entertained with good reason. The history of onset after freezing of the parts and the recurrence of the lesions during the colder seasons suggest the diagnosis of pernio. There are several varieties of pernio, two of which are called lupus pernio. The first or chilblain lupus, with which Hutchinson's name is linked, is a form of lupus erythematosus. It consists of infiltrated erythematous patches which become worse in the winter. The lesions are bluish red or violaceous, which first resemble chilblains and discoid lupus erythematosus. The second type of lupus pernio, the one associated with Besnier's name, is classified with sarcoidosis. Its lesions occur symmetrically on the ears and face, hands and feet and are thickened, bluish red patches. They show small brownish red nodules by diascopic pressure. Small dilated blood vessels are present and many manifestations of sarcoidosis may be associated, such as changes in the small bones and enlargement of the lymph glands. Both kinds of lupus pernio do not disappear entirely in the summer, though they may improve considerably. In the case under consideration the skin changes apparently disappear entirely during the warmer months. It is more likely, therefore, that the condition is ordinary pernio or chilblains. It disappears entirely in summer and is based on a poor circulation. The lesions are various shades of red, feel tender and may burn or itch. They feel cold to the touch.

This patient should be investigated for tuberculosis. His circulation should be improved by physical therapy, exercise and massage. Warm clothing should be worn and the parts protected by cotton batting and local applications. Dusting powders of borated talcum are useful or the parts may be painted with ichthammol. The administration of arsenic is helpful and may be given in the form of solution of potassium arsenite or the asiatic pill.

POSSIBLE KIDNEY DAMAGE AND LATE HYPERTENSION FROM KEROSENE

To the Editor:—A white, single woman aged 25 was seen four months ago for the first time because of an attack of dyspnea and edema. She then weighed 185 pounds (84 Kg.) and now weighs 170 pounds (77 Kg.). She had an elevated blood pressure of 240/120, which has remained approximately the same. Her urine showed 4 plus albumin; intermittently since then the urine has been completely free from albumin. Blood chemistry showed nonprotein nitrogen of 42, creatine 1.3 and cholesterol 220 mg. I do not believe any hyperthyroidism exists; basal metabolic tests read plus 23 and plus 26. Cystoscopy showed a normal bladder and bladder mucosa. A number 6 French catheter was inserted into each kidney pelvis without resistance, and no residual urine was found. Specimens were clear. A plain x-ray film showed no radiopaque stone in the kidneys, ureter or bladder, and bilirenal pyelograms were normal. Nothing has been found except the hypertension and the intermittent albumin in the urine. The family history on both sides is negative for hypertension. In the past history of the patient there is one factor which may have a bearing on the hypertension. When about 6 years old she drank an ounce or so of kerosene. Could the kerosene have damaged her kidneys at the time? Are there any studies on kerosene taken orally damaging the kidneys?

M.D., South Carolina.

ANSWER.—Oral poisoning by kerosene usually is considered in conjunction with such other petroleum fractions as naphtha, gasoline and mineral spirits. Clinical manifestations are similar but not necessarily identical. The mortality from gasoline is much higher than from kerosene. At times the ingestion of sizable amounts (exact amounts frequently unknown) is followed by no untoward events. Conversely, smaller quantities have on occasion caused death. Early symptoms are chiefly related to the gastrointestinal tract, such as burning pain in the throat and stomach, vomiting, intestinal pain, diarrhea and great thirst; other effects are dyspnea, cyanosis, drowsiness, nephritis, cystitis and at times elevated temperature. Some survivors may exhibit prolonged significant sequelae. In the case mentioned, much depends on the extent of total damage soon after the kerosene ingestion. If extensive, it is permissible to assume that kidney damage probably existed at that time. Many reports have been made on this subject, not all of which mention nephritis.

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McNally, W. D.: Toxicology, *Industr. Med.*, Chicago, 1937.

INCONTINENCE AFTER TEAR OF SPHINCTER FROM CHILDBIRTH

To the Editor:—In the case of some fistulas in ano it is said, and I have known this to be true, that the sphincter can be cut at any place in its circumference and at any angle and healing will occur without incontinence provided the area is not packed longer than twenty-four hours. Why will incontinence always occur after a tear through the sphincter following childbirth?

Major, M. C., A. U. S.

ANSWER.—Incontinence follows a tear through the sphincter following childbirth because the perineal body is torn into which the sphincter muscles attach themselves anteriorly. This allows the sphincters to open when they contract rather than to make a closure. This results in incontinence.

CLEFT PALATE AT SIXTEEN

To the Editor:—A patient aged 16 has a cleft palate. The posterior two thirds of the hard palate has an aperture about 1.5 cm. wide. What would be the prognosis if corrective surgery should be attempted at this time and what improvement in speech defect might be expected?

A. A. Shamp, M.D., La Crosse, Wis.

ANSWER.—The development of the musculature of the upper part of the pharynx will largely determine the result of a simple operation of closing the palate. In all probability the palate can be closed unless much tissue has been lost from previous operations.

Where the muscle action mentioned is deficient, a much better speech result can be obtained by special speech training or, if necessary, by lengthening the palate by further surgery. This had best be done by some one familiar with this work.

Some idea of the muscle activity can usually be gained by depressing the tongue and stimulating the posterior wall of the upper pharynx by pressing on it with a cotton applicator and observing the contraction at the junction of the nasopharynx with the oropharynx

BLISTER BUGS AND CHIGGERS

To the Editor:—In the August 7 issue of The Journal, page 1054, a lieutenant from the Medical Corps, Army of the United States, describes a vesicular eruption occurring presumably after the bite of an insect. In addition he asks whether there is any insect called a blister bug. In the reply the statement is made that no blister bug is known. In this regard bites are not infrequent from a beetle called locally a "blister beetle." These are of the family Meloidae, species Cantharis vesicatoria. More commonly these beetles are spoken of as a Spanish fly. The active irritant from this insect is cantharidin, which is a well known vesicant. The bite from this beetle is painful and results in an erythema and a cluster of vesicles. It is not impossible that the lesion described by the lieutenant may result from a bite by this beetle. As far as I know there is no specific treatment.

Ransdell Garvey, Captain, M. C., A. U. S.

To the Editor:—Some one asks if there is any insect called a "blister bug." Your editor replies "No blister bug is known; possibly that name might be applied to the chigger." This is utter nonsense; blister beetles are very common in this section. If my brother Will were here he would tell me the Latin name for them; they belong to the family Cantharidae, which ought to strike up a live association in the mind of your esteemed dermatologic editor. They are a narrow, elongated beetle with a red thorax. Both the bite and the crushing of the insect against the skin cause pain, vesicle formation and itching. My sister has a half dozen vesicles on her leg at the present moment and my wife has one on her neck. Every farmer knows them, every rural doctor knows them, and I have a suspicion that one or two doctors in Chicago know them.

Karl Menninger, M.D., Topeka.

To the Editor:—There are two organisms locally known or included under the name of "chigger"—originally spelled jigger. One is the larva of an arachnoid which goes under the name of harvest mite, harvest bug, harvest mite, as you state. This is a relatively unimportant organism which is active in the fall of the year chiefly; hence the name harvest mite. The other one is an insect belonging to the genus of the subfamily Sarcopsyllinae. It is a minute insect and is seldom seen even by its victims. It is only about 1/24 inch long. The fleas which frequent burrow beneath in the skin. The active period of the insect is about sixty days beginning the latter part of June. It is so bad in this section of the country during July that some men give up their golf during the chigger season. It is a real problem both for the reason of the great discomfort it causes and from the fact that the bites sometimes become infected and lead to abscesses. The chigger gets on its victim from the grass, so that the application of any preventive must be as high as any grass which one is likely to come in contact with and must be applied to all parts of the body which will come in contact with grass. For example, pantaloon should apply the preventive up to the ankle if they are going to sit on the ground. The chigger attacks any part of the body it reaches. The feet are frequent sites of attack. The common preventives are kerosene and sulfur, which must be applied to the feet and legs as high as the groin, or higher.

I have experimented with several "chigger sheets." I found that an application of Kress Dip, ten drops to a cup of water, rubbed on my legs up to my knees would allow me freedom from chiggers even when hunting my ball in the rough. One difficulty with sulfur dusted in the hose or on the legs is that if one perspires freely, as one does on the golf course during the chigger season, the perspiration seems to wash off the sulfur. I have found that sublimated sulfur mixed with vaseline and rubbed on is much better and surer preventive. With any preventive the application must be as high as the groin with which one comes in contact. The chigger bite is at first scarcely discernible and its presence is manifest by a mild itching, which becomes intense on scratching. The scratching seems to augment the edema and before one realizes it one has denuded an area from 1 to 2 millimeters in diameter. The itching continues for about a week, especially when parts of the body covered by clothing are exposed to the air. Continued scratching enlarges the denuded areas until they are usually 5 mm. in diameter or larger. The legs of country children are frequently dotted with these scabs during the chigger season.

The other statement in your answer that needs revision is in regard to the blister bug. You know that it is a common practice to call every insect that flies a fly, and every insect that crawls a bug. There is an insect, a beetle, that has been known since medieval times as the "blister beetle." It is also known as the Spanish fly. Of course, in the entomologic sense it is not a bug since this name is reserved for members of the Heteroptera, while beetles belong to the Coleoptera; therefore your answer is technically correct. But, as said, this beetle has been called the blister beetle, or blister bug, since medieval times. It gets its name from the fact that if the insect is dried and the powder made into a poultice and applied to the skin it will cause erythema or even vesication. It was once a valued item in the physician's armamentarium. It is reported that if the insect is crushed on the skin and the "juice" is not removed a "blister" will form in the site.

L. A. Turley, Ph.D., Oklahoma City.
Professor of Pathology, University of Oklahoma.

LEFT HANDEDNESS

To the Editor:—In The Journal, June 26, 1943, page 642, an inquiry and an answer appeared concerning lefthandedness. I disagree slightly with the advice given. Parents should not encourage the child to use the right hand in eating but permit her to work out her own salvation. She may find social embarrassment in left handed writing or left footed dancing. The persons answering the question properly stated that "ill effects may follow if a predominantly left handed child is forced to use the right hand." If a child is 3 years old it should not be difficult to determine the hand that she voluntarily uses for eating and writing. There may be advantages in determining whether she has right or left eye dominance in determining her future education. At the present time, however, she should be permitted to have the complete emergence of her structural preference.

Ira S. Wile, M.D., New York.

JOURNALS ABSTRACTED IN THE CURRENT MEDICAL LITERATURE DEPARTMENT, MAY-AUGUST 1943

Titles have been listed or abstracts made of important articles in the following journals in the Current Literature Department of THE JOURNAL during the past four months. Any of the journals, except those starred, will be lent by THE JOURNAL to subscribers in continental United States and Canada and to members of the American Medical Association for a period not exceeding three days. Three journals may be borrowed at a time. No journals are available prior to 1933. Requests for periodicals should be addressed to the Library of the American Medical Association and should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Thus most of these journals are accessible to the general practitioner.

Arción Médica. La Paz.
Acta Medica. Rio de Janeiro.
American Heart Journal. St. Louis.
American Journal of Clinical Pathology. Baltimore.
American Journal of Digestive Diseases. Fort Wayne, Ind.
*American Journal of Diseases of Children. A. M. A., Chicago.
American Journal of Hygiene. Baltimore.
American Journal of the Medical Sciences. Philadelphia.
American Journal of Obstetrics and Gynecology. St. Louis.
American Journal of Ophthalmology. Cincinnati.
American Journal of Orthopsychiatry. New York.
American Journal of Pathology. Ann Arbor, Mich.
American Journal of Physiology. Baltimore.
American Journal of Psychiatry. New York.
American Journal of Public Health. New York.
American Journal of Roentgenol. and Radium Therapy. Springfield, Ill.
American Journal of Surgery. New York.
American Journal of Syphilis, Gonor. and Venereal Diseases. St. Louis.
American Journal of Tropical Medicine. Baltimore.
American Review of Tuberculosis. New York.
Anais da Faculdade de medicina da Universidade de São Paulo. São Paulo.
Anales de la Cátedra de clinica ginecológica. Rosario.
Anesthesiology. New York.
Annales Paediatrici. Basel.
Annals of Internal Medicine. Lancaster, Pa.
Annals of Otology, Rhinology and Laryngology. St. Louis.
Annals of Surgery. Philadelphia.
*Archives of Dermatology and Syphilology. A. M. A., Chicago.
Archives of Disease in Childhood. London.
*Archives of Internal Medicine. A. M. A., Chicago.
*Archives of Neurology and Psychiatry. A. M. A., Chicago.
*Archives of Ophthalmology. A. M. A., Chicago.
*Archives of Otolaryngology. A. M. A., Chicago.
*Archives of Pathology. A. M. A., Chicago.
*Archives of Surgery. A. M. A., Chicago.
Archivos argentinos de pediatria. Buenos Aires.
Archivos de medicina infantil. Havana.
Army Medical Bulletin. Washington, D. C.
Boletin de la Sociedad Cubana de Pediatria. Havana.
Brain. London.
British Heart Journal. London.
British Journal of Children's Diseases. Dorking, England.
British Journal of Dermatology and Syphilis. London.
British Journal of Experimental Pathology. London.
British Journal of Ophthalmology. London.
British Journal of Radiology. London.
British Journal of Surgery. Bristol.
British Journal of Tuberculosis. London.
British Journal of Urology. London.
British Medical Journal. London.
Bulletin of the Health Organization of the League of Nations. Geneva.
Bulletin of the Johns Hopkins Hospital. Baltimore.
Bulletin of the Los Angeles Neurological Society.
Bulletin of the New York Academy of Medicine. New York.
California and Western Medicine. San Francisco.
Canadian Medical Association Journal. Montreal.
Canadian Public Health Journal. Toronto.
Cancer Research. Baltimore.
Confinia Neurologica. Basel.
Connecticut State Medical Journal. Hartford.
Delaware State Medical Journal. Wilmington.
Deutsche medizinische Wochenschrift. Leipzig.
Diseases of Chest. Chicago.
Edinburgh Medical Journal.
Endocrinology. Springfield, Ill.
Experimental Medicine and Surgery. Brooklyn.
Hawaii Medical Journal. Honolulu
Helvetica medica acta. Basel.
Illinois Medical Journal. Chicago.
Journal of Allergy. St. Louis.
Journal of the Arkansas Medical Society. Fort Smith.
Journal of Bone and Joint Surgery. Boston.
Journal of Clinical Endocrinology. Springfield, Ill.
Journal of Clinical Investigation. Boston.
Journal of Experimental Medicine. New York.
Journal of the Florida Medical Association. Jacksonville.
Journal of Immunology. Baltimore.
Journal of the Indiana State Medical Association. Indianapolis.
Journal of Industrial Hygiene and Toxicology. Baltimore.
Journal of Infectious Diseases. Chicago.
Journal of Investigative Dermatology. Baltimore.
Journal of the Iowa State Medical Society. Des Moines.
Journal of the Kansas Medical Society. Topeka.
Journal of Laboratory and Clinical Medicine. St. Louis.
Journal-Lancet. Minneapolis.
Journal of the Maine Medical Association. Portland.
Journal of the Medical Association of the State of Alabama. Montgomery.
Journal of the Medical Association of Georgia. Atlanta.
Journal of the Medical Society of New Jersey. Trenton.
Journal of Mental Science. London.
Journal of the Michigan State Medical Society. Lansing.
Journal of the Missouri State Medical Association. St. Louis.
Journal of the Mount Sinai Hospital. New York.
Journal of the National Cancer Institute. Washington, D. C.
Journal of Nervous and Mental Disease. New York.
Journal of Neuropathology and Experimental Neurology. Baltimore.
Journal of Neurophysiology. Springfield, Ill.
Journal of Nutrition. Philadelphia.
Journal of Obstetrics and Gynaecology of British Empire. Manchester.
Journal of the Oklahoma State Medical Association. Oklahoma City.
Journal of Pathology and Bacteriology. Edinburgh.
Journal of Pediatrics. St. Louis.
Journal of Pharmacology and Experimental Therapeutics. Baltimore.
Journal of Physiology. Cambridge.
Journal of Royal Army Medical Corps. London.
Journal of Royal Naval Medical Service. London.
Journal of the South Carolina Medical Association. Florence.
Journal of the Tennessee State Medical Association. Nashville.
Journal of Thoracic Surgery. St. Louis.
Journal of Urology. Baltimore.
Kentucky Medical Journal. Bowling Green.
Klinicheskaya meditsina. Moscow.
Klinische Wochenschrift. Berlin.
Lancet. London.
Laryngoscope. St. Louis.
Lekarz Wojskowy. Edinburgh.
Medical Annals of the District of Columbia. Washington.
Medical Journal of Australia. Sydney.
Medicina española. Valencia.
Military Surgeon. Washington, D. C.
Minnesota Medicine. St. Paul.
Münchener medizinische Wochenschrift. Munich.
Nature. London.
Nebraska State Medical Journal. Lincoln.
New England Journal of Medicine. Boston.
New Orleans Medical and Surgical Journal.
New York State Journal of Medicine. New York.
North Carolina Medical Journal. Winston-Salem.
Northwest Medicine. Seattle.
Ohio State Medical Journal. Columbus.
Ophthalmologica. Basel.
Pediatria de las Américas. Mexico, D. F.
Pediatria e Puericultura. Bahia.
Pennsylvania Medical Journal. Harrisburg.
Physiological Reviews. Baltimore.
Practitioner. London.
Prensa Médica Argentina. Buenos Aires.
Presse médicale. Paris.
Psychosomatic Medicine. Baltimore.
Public Health Reports. Washington, D. C.
Quarterly Journal of Medicine. Oxford.
Radiologia. Buenos Aires.
Radiology. Syracuse, N. Y.
Review of Gastroenterology. New York.
Revista Argentina de neurologia y psiquiatria. Rosario.
Revista de la Asociación Médica Argentina. Buenos Aires.
Revista clinica española. Madrid.

*Cannot be lent.

Revista médica de Chile. Santiago.
Revista médica latino-americana. Buenos Aires.
Revista Medica de Rosario. Rosario.
Revista de neurologia y psiquiatria de São Paulo. São Paulo.
Revista de neuro-psiquiatria. Lima.
Revista Paulista de Medicina. São Paulo.
Revista de la Policlinica Caracas. Caracas.
Rhode Island Medical Journal. Providence.
Rocky Mountain Medical Journal. Denver.
Schweizerische medizinische Wochenschrift. Basel.
Schweizerische Zeitschrift für Pathologie und Bakteriologie. Basel.
Semana médica. Buenos Aires.
South African Medical Journal. Cape Town.
Southern Medical Journal. Birmingham, Ala.
Southwestern Medicine. Phoenix, Ariz.
Surgery. St. Louis.
Surgery, Gynecology and Obstetrics. Chicago.
Texas State Journal of Medicine. Fort Worth.
Transactions of the Royal Society of Tropical Medicine and Hygiene. London.
United States Naval Medical Bulletin. Washington, D. C.
Virginia Medical Monthly. Richmond.
Voprosy Neyrokhirurgie. Moscow.
*War Medicine. A. M. A., Chicago.
Western Journal of Surgery, Obstetrics and Gynecology. Portland, Ore.
West Virginia Medical Journal. Charleston.
Wiener klinische Wochenschrift. Vienna.
Wisconsin Medical Journal. Madison.
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SUBJECT INDEX

This is an index to all the reading matter in THE JOURNAL. In the Current Medical Literature Department only the articles which have been abstracted are indexed.

The letters used to explain in which department the matter indexed appears are as follows: "BI," Bureau of Investigation; "E," Editorial; "C," Correspondence; "OS," Organization Section; "ab," abstracts; the star (*) indicates an original article in THE JOURNAL.

This is a subject index and one should, therefore, look for the subject word, with the following exceptions: "Book Notices," "Deaths," "Medicolegal Abstracts" and "Societies" are indexed under these titles at the end of the letters "B," "D," "M," and "S." State board examinations are entered under the general heading State Board Reports, and not under the names of the individual states. Matter pertaining to the Association is indexed under "American Medical Association." The name of the author, in brackets, follows the subject entry.

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A.—Association	*Pharm.—Pharmaceutical*
Coll.—College	*Phys.—Physicians*
Conf.—Conference	*Rev.—Revision*
Cong.—Congress	*Ry.—Railway*
Conv.—Convention	*Soc.—Society*
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